



THE UNIVERSITY *of* TEXAS
MEDICAL SCHOOL AT HOUSTON

A part of The University of Texas Health Science Center at Houston



**2008 SUMMER RESEARCH PROGRAM
STUDENT ABSTRACTS**

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Preface

The University of Texas at Houston Medical School (UTHMS) 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 teachers. 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 1,600 medical, college, and international medical students have gained research experience through the UTHMS 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.

UTHMS student research training is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and/or by financial support from the Dean and the departments and faculty of the Medical School.

Science education remains a vital and integral part of our nation's interests. The UTHMS 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 scientific communities.



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

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Acknowledgements

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

Indicative of this support is the administrative assistance and financial support provided by the UTHMS. Sincere appreciation is expressed to Dean Giuseppe Colasurdo M.D., Patricia M. Butler, M.D., Associate Dean, Office of Educational Programs, and to L. Maximilian Buja, M.D., Executive Vice President for Academic Affairs who continue to insure the yearly success of the Summer Research Program.

Major financial assistance for our Program has also been provided by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) through a short-term research grant (5 T32 DK007676).

Dr. Bryant Boutwell, Associate Vice President for International Programs and Accreditation, has negotiated cooperative agreements with several international medical schools to set up tailored programs for selected international medical students. This international initiative provides the opportunity for our Program to participate in a new area of research education that will be expanded in years to come.

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

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Lab Research Ownership

Publication and/or Disclosure

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

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

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

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

2008 Summer Research Program
University of Texas at Houston Medical School Students

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MEDICAL STUDENTS

ABSTRACT

Prognostic Utility of the Pre-Hospital 12 Lead Electrocardiogram in Acute Anterior Myocardial Infarctions

ROBERT A. AERTKER *The University of Texas at Houston Medical School Class of 2011*

Sponsored by: Richard W. Smalling, M.D., Ph.D.
Department of Internal Medicine – Division of Cardiology

Supported by: Richard W. Smalling, M.D, Ph.D.
University of Texas Medical School at Houston – Office of the Dean

Key Words: Electrocardiogram, ST elevation, myocardial infarction, proximal LAD

Objectives: This study sought to determine if the 12 lead electrocardiogram (ECG) is capable of predicting proximal left anterior descending (LAD) artery occlusions.

Background: Acute anterior myocardial infarctions caused by proximal LAD occlusions are associated with a higher morbidity and mortality when compared to non-proximal LAD occlusions. Identification of these high risks patients via the 12 lead ECG will assist physicians in providing care for patients with ST elevation myocardial infarctions.

Methods: In a post-hoc analysis of the PATCAR pilot trial data, we compared the ECG findings of proximal (proximal to the first septal perforator) and non-proximal (distal to the first septal perforator) LAD occlusions for patients who had an ECG performed within 180 minutes of symptom onset.

Results: In patients with ECG's performed within 60 minutes of symptom onset, a sum ST elevation (STE) ≥ 12.5 mm in leads V1 -6 had a sensitivity of 52.3%, specificity of 92.9%, positive predictive value of 91.7%, and negative predictive value of 56.5% for predicting proximal LAD occlusions. In this same patient group, a sum STE plus the absolute value of ST depression in II, III, and aVF of ≥ 17.5 mm had a sensitivity of 57.1%, specificity of 92.9%, positive predictive value of 92.3%, and negative predictive value of 59.1% for predicting proximal LAD occlusions.

Conclusions: The sum STE (V1-6) and the sum STE (V1-6) + sum ST depression (II, III, aVF) on a 12 lead ECG can be used to predict proximal LAD occlusions if performed within the first hour of symptom onset and high sum STE or STE + ST depression values should be considered high risk findings. Furthermore, culprit artery patency can not be predicted using ST deviations.

ABSTRACT

Cerebrospinal fluid from Parkinson disease patients differentially affects alpha-synuclein density and cell growth in microglia compared to astrocytes

JENNIFER BARNES

The University of Texas at Houston Medical School Class of 2011

Sponsored by: Mya Schiess, MD, Department of Neurology

Supported by: Kanaly Foundation for Parkinson's disease Research
University of Texas Medical School at Houston - Office of the Dean

Key Words: PD, microglial cell, astrocyte, alpha-synuclein, fluorescence

A neuroinflammatory process has been implicated in the pathoetiology of idiopathic Parkinson's disease (PD). It is postulated that increased expression of proinflammatory cytokines by activated microglia alter the formation and distribution of the PD associated intracellular protein alpha-synuclein (α -synuclein). Our preliminary studies suggested that cultured glial cells exposed to cerebrospinal fluid (CSF) from patients with PD show loss of cellular adhesion and a necrotic death. This study explores the effects of CSF from PD patients on two functionally different glial cell lines by monitoring growth, recovery, α -synuclein content and intracellular distributions compared to untreated cells. We hypothesize that loss of cell adhesion is related to loss of function from excess or dysfunctional α -synuclein. Microglia cells obtained from human brain glioblastoma cells and astrocytes from fetal brain tissue were cultured, grown to confluence, treated with fixed concentrations of CSF, photographed and fluorescently probed for α -synuclein, actin, and nuclei over a range of 0-9 days. Our results show that astrocyte growth rates are reduced by exposure to PD CSF, with α -synuclein content inconsistently affected, but a trend toward a dispersed α -synuclein distribution compared to localization in the peripheral processes in controls. However, cultured microglia cells exhibited reduced cell growth and loss of adhesion that correlated with increased α -synuclein content, which additionally was redistributed from a cytoplasmic to a peri-nuclear location. Treated microglial cells recovered with robust growth when replenishment of media was performed. These results support our hypotheses of excess α -synuclein contributing to loss of cell function and eventual necrotic cell death.

ABSTRACT

Metabolic Parameters for Cranioplasty Resorption following Decompressive Craniectomy

ALISON B BARROW

The University of Texas at Houston Medical School Class of 2011

Sponsored by: Mary Ruppe, M.D., Department of Internal Medicine

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

Key Words: Autograft Cranioplasty; Decompressive Craniectomy; Bone Flap, Resorption

When traumatic brain injury results in increased intracranial pressure, measures are taken to improve the cerebral perfusion pressure. If conservative measurements fail, decompressive craniectomy is frequently performed. If the patient survives, autologous cranioplasty provides economic and biological benefits to repair the skull defect. One complication following such cranioplasty is resorption of the autologous bone flap, with rates of 50-100% being reported. Beyond cosmetic concerns, bone flap resorption presents many metabolic complications, including hypercalcemia and nephrolithiasis. It is theorized that resorption occurs when there is a mismatch between the remodeling activity of the surviving osteoclasts and the bone formation by the surviving pre-osteoblasts. For our study, we developed a system to model the timing parameters of cranioplasty resorption and constructed a database to evaluate metabolic, nutritional, demographic and pharmacologic parameters that may contribute to the resorption. Laboratory and Computed Tomography data was obtained from 8 adolescent subjects during their treatment for traumatic brain injury. Utilizing the software Analysis of Functional Neuroimages (AFNI), we developed a method to calculate the density and volume loss in the bone flaps over time. This involved registering the CT data and thresholding for a density range of bone while excluding any artifacts such as surgical staples and CSF shunts that possibly fell within this range. Correlating this information to database parameters during the same time course will reveal metabolic contributors to the resorption and allow us to assess risk factors for bone loss following autograft cranioplasty. In addition, this data will help establish a potential window for therapeutic intervention in future patients.

ABSTRACT

Identification of the causative bacteria in diabetic foot ulcer infections by 16S rDNA detection

ALAN L BLANKENSHIP *The University of Texas at Houston Medical School Class of 2011*

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

Supported by: Orthopaedic Research and Education Foundation
University of Texas Medical School at Houston – Office of the Dean

Key Words: Diabetes, diabetic foot ulcer infections, 16S rDNA, bacterial pathogens

Diabetes mellitus is increasing by epidemic proportions and is a major health care burden worldwide. Diabetic foot ulcer infections (DFUI) are a leading cause of hospitalization of the more than 20 million diabetic Americans. DFUI, which result from persistent polymicrobial surface-associated infections of the soft tissue and bone, are termed biofilm infections and are difficult to treat. Standard laboratory cultivation and identification methods appear to be inadequate for the isolation of the causative agents of DFUI. However, molecular techniques, such as 16S rDNA detection analysis using primers for the conserved regions of the bacterial 16S rRNA gene offer an alternative approach for identification of these pathogens. This technique is especially useful in that it can detect non-culturable bacteria and those in low abundance. In this study ten tissue samples were collected from patients with DFUI. The 16S rDNA PCR assay was performed and DNA sequence analysis was used to identify the predominant infectious agents. In six of the samples the predominating 16S rRNA gene was encoded by a bacterium not isolated in the clinical laboratory. Interestingly, four of the six bacteria were anaerobes. These data reveal the effectiveness of 16S rDNA analysis to identify new bacteria as causative agents of DFUI. In addition, the denaturing gradient gel electrophoresis (DGGE) method to separate PCR products amplified from polymicrobial samples based on their %GC content, rather than their size, was optimized. It was used successfully to separate the pathogenic bacteria in a tissue sample for subsequent DNA sequence analysis and identification.

ABSTRACT

Identification of miRNAs Mediating TGF- β Induced Apoptosis in Intestinal Epithelial Cells

MATTHEW W. BROSSEIT *The University of Texas at Houston Medical School* Class of 2011

Sponsored by: Tien Ko, MD, Department of Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15; Tien C. Ko: NIH R01 DK60105 "Study of growth regulation in surgical diseases of the gut"; University of Texas Medical School at Houston – Office of the Dean

Key Words: miRNA, TGF- β , smad3

Background:

MicroRNAs (miRNAs) are small noncoding RNA molecules that regulate the expression of genes by base-pairing with their target messenger RNAs. Since the discovery of the first miRNA in 1993, it has been shown that miRNAs play fundamental roles in the regulation of diverse biological processes including cell growth and differentiation, apoptosis, and embryonic development. Previously, we have shown that TGF- β induces apoptosis in rat intestinal epithelial cells (RIE-1) through caspase 3 activation, and overexpression of Smad3 enhances TGF- β -induced apoptosis. We hypothesize that TGF- β induces apoptosis through regulation of a set of miRNAs and restoration of the expression of these miRNAs would inhibit TGF- β -induced apoptosis in intestinal epithelial cells.

Design:

Three cell lines derived from the same parental RIE-1 cells, i.e. RIE-1/Smad3 (RS3) which overexpresses functional Smad3, RIE-1/dnSmad3 (RS3 Δ) which expresses a dominant negative mutant of Smad3 and RIE-1/Akt (RAkt) which overexpresses constitutively activated Akt to block apoptosis induction were used in this study. The response of RS3 and RS3 Δ cells to TGF- β was confirmed by Western blot analysis and Cell Death Detection (CDD ELISA from Roche). Total RNAs were then isolated from TGF- β - and vehicle-treated RS3, RS3 Δ and RAkt cells and microRNA profiling was performed using miRCURY LNA™ microRNA Arrays (Exiqon).

Results:

Western blot analysis showed that in the presence or absence of TGF- β , Smad3 was expressed at a similar level in both RS3 and RS3 Δ cells, however, TGF- β treatment resulted in significant phosphorylation (activation) of Smad3 in RS3 cells as compared to very low levels of phosphorylation of Smad3 in RS3 Δ cells. CDD analysis showed that TGF- β induced a 6.3-fold increase in apoptosis in RS3 cells as compared with only a 1.9-fold increase in RS3 Δ cells. The microarray data revealed that in the RS3 cells, 105 miRNAs showed at least a two-fold difference in expression between the TGF- β and vehicle-treated groups. Among them, 36 were changed only in TGF- β -treated RS3 cells, but not the control cells. Of the 36 miRNAs regulated by TGF- β , 20 miRNAs were upregulated and 16 downregulated by TGF- β treatment. By searching internet databases and literature, we identified a number of these miRNAs whose known activity and possible targets make them strong candidates for miRNAs that may be crucial to TGF- β -induced apoptosis.

Future Research:

TGF- β -regulated microRNAs will be validated using real-time quantitative RT-PCR and their function in apoptosis induction will be confirmed by specific miRNA inhibitors and overexpression of specific miRNAs in RS3 or RS3 Δ cells using transient transfection.

ABSTRACT

Murine Glomerular Podocyte Expression of Complement Regulatory Proteins

KATHERINE BURT

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Supported by: Michael C. Braun, Department of Pediatrics

Supported by: Michael C. Braun, Department of Pediatrics
University of Texas Medical School at Houston – Office of the Dean

Key Words: Podocyte, Complement, CRP

The complement system is regulated by over 20 distinct proteins. These can be classified as either fluid phase complement regulatory proteins (sCRP) or membrane bound regulatory proteins (mCRP). Recent evidence has suggested that tissue specific patterns of CRP expression may influence complement mediated end organ damage. This study sought to characterize the specific pattern of CRP expression in cultured glomerular epithelial cells (podocytes).

To measure CRP expression, total RNA was harvested from cultured primary murine podocytes. RNA was reverse transcribed and the expression of all 20 currently recognized CRP was determined using real time PCR. Gene expression was normalized to the housekeeping gene GAPDH. Of the 20 possible CRP mRNAs, only 6 were expressed in podocytes. mRNA for the mCRP: CD59a, Crry, and MCP, as well as the sCRP: C4bp, FH, and Clusterin were detected using quantitative PCR. CD59a, Crry, MCP, and Clusterin were all expressed at levels similar to those found in normal liver tissue. FH and C4bp were expressed at 700 fold and 30 fold lower levels than in normal liver. Crry and CD59a expression was confirmed using immunofluorescent staining of podocytes grown in culture.

These data indicate that the pattern of expression of complement regulatory proteins in glomerular podocytes is restricted and differs significantly from the pattern of expression found in liver tissue. The paucity of CRP expression in podocytes may be due to the minimal exposure of podocytes *in vivo* to plasma proteins, and thus reflect a limited need for regulation of locally synthesized complement components.

ABSTRACT

The Effect of Weight Loss on Psoriasis Area Severity Index in Adult Psoriasis

RACHEL WERGIN

The University of Texas at Houston Medical School Class of 2011

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

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16

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

Key Words: Psoriasis, weight loss, obesity

Psoriasis is a systemic inflammatory disease that affects 3% of the population and causes a significant amount of physical and psychological distress to those affected. 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 and oligoarthritis characteristic of the disease. Cytokine mediated inflammation, present in both psoriasis and obesity, raise the risk of developing myocardial infarction and the metabolic syndrome. Developing psoriasis is directly related to Body Mass Index (BMI) as determined by the formula: $\text{weight (kg)} / \text{height}^2 (\text{m}^2)$. A clinical trial was designed to evaluate the effect of weight loss on the severity of psoriasis in adult patients. A total of twenty male and female participants with moderate to severe plaque psoriasis and a $\text{BMI} \geq 25$ are to be enrolled in a 6 month program of weight loss counseling. Baseline evaluation will include assessment of BMI 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 physician guided weight loss program to include individual nutritional and physical activity counseling. Psoriasis severity will be reevaluated at weeks 6, 12, 18, and 24. Primary outcome measures will determine the mean change in PASI score from baseline to 24 weeks. Secondary outcome measures will assess the amount of weight loss achieved and the subject's assessment of overall improvement of psoriasis.

ABSTRACT

Assessment of Venous Access in Pediatric Emergency Care Facilitated by Veinlite Technology with Reduced Pain and Time and Without Extensive Experience

MATTHEW K. CHINN *The University of Texas at Houston Medical School Class of 2011*

Sponsored by: Christine E. Koerner, MD
Department of Emergency Medicine

Supported by: University of Texas Health Science Center – Office of the Executive Vice-President for Academic Affairs
University of Texas Medical School at Houston – Office of the Dean

Key Words: Veinlite, pediatrics, emergency medicine, transillumination, venous access

Background

Venous access in children can be difficult to achieve. Frey and Lininger demonstrated a 44% and 53% venous access success rate for RNs, respectively. Katsogridakis, et, al, showed statistical significance with transillumination (Veinlite) assisted venous access over standard access. The purpose of this pilot study is to determine whether Veinlite can facilitate venous access in children.

Methods

The study was conducted from June 9-13, 2008 (0700-1900), at a pediatric emergency center (0-21 years) serving an indigent population. All patients needing cannulation were eligible, except critical patients. Nurses were trained in the use of the Veinlite. Twenty-five envelopes were randomly assigned as Veinlite or Standard. The nurse chose an envelope and performed the indicated technique up to two times. Should the nurse fail at both attempts, another nurse continued the study. Patient data was obtained including body mass index (BMI), skin color, dehydration level, and prior cannulation history. Nurses provided information regarding cannulation experience and difficulty level of the procedure.

Results

Successful venous access on the first attempt was 83.33% with the transillumination versus 76.92% with the standard technique. Venous access was obtained in all patients within three attempts. There was no statistically significant difference between the two techniques in predicting successful venous access.

Method	Patient Age (years)	Patient BMI	Nursing Experience (years)	Difficulty Assessment Scale (0-5)	Avg. # of Attempts
Veinlite	11.68	23.41	4.33	3.33	1.33
Standard	6.03	21.54	7.00	2.38	1.23
All	8.74	22.44	5.72	2.84	1.28

Conclusion

This study was limited due to the small sample size. Nurses with experience in cannulation showed no significant benefit with the use of the device. However, further studies should be done to determine the Veinlite's potential as an educational tool for inexperienced healthcare workers.

ABSTRACT

A Model For the Quantization of Re-Epithelialization of Partial Thickness Burn Injuries

PATRICK A COCKERILL The University of Texas at Houston Medical School Class of 2011

Sponsored by: David J Wainwright, MD
Department of Plastic Surgery

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

Key Words: Partial Thickness Burn

The epidermal healing process following a burn injury occurs by migration of keratinocytes from the wound edges and proliferation of epithelium from pilosebaceous units and eccrine glands. A partial thickness burn wound that spares these deep structures utilizes both methods of re-epithelialization. Attempts to quantitate this re-epithelialization have been limited. The purpose of this study is to create a model for the quantization of the reepithelialization of partial thickness wound healing.

The attending surgeon identified suitable partial thickness injuries and serial pictures were taken with a Nikon D100 camera using an SB600 flash connected by a SC-29 cord. Pictures were uploaded into Adobe Photoshop to optimize brightness and contrast, and then analyzed using an image analysis program (Image J, NIH). The images were calibrated using a millimeter ruler present in each photograph. Using specific landmarks, a consistent area was analyzed once the image was rotated and cropped. The wound edge was traced using a Wacom Graphire tablet and measured, and the epithelial islands were traced, thresholded, and measured using the Analyze Particles command. The result is a measure of the area of migrated epithelium from the wound edge and epithelial islands.

This model provides an accurate and comprehensive measurement of epithelialization of partial thickness burn wounds, by including migration from the wound edge and hair follicles and glands. This model will be applied to future studies examining the healing process between different patient populations.

ABSTRACT

Visualization of *Staphylococcus aureus* after Osteoblast Invasion

PAIGE L COHICK

The University of Texas at Houston Medical School Class of 2011

Sponsored by: Catherine G. Ambrose, Ph.D., Department of Orthopaedic Surgery;
Heidi B. Kaplan, Ph.D. Department of Microbiology and Molecular Genetics

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16 ; University of Texas Medical School at Houston - Office of the
Dean

Key Words: GFP *S. aureus*, diabetic foot ulcer infection

Diabetic Foot Ulcer Infections are the most common reason for a diabetic patient to visit the hospital and the invading polymicrobial infections are challenging to treat. Previous stains to identify *S. aureus* in an in vitro diabetic foot ulcer biofilm model such as SYTO green and propidium iodide would be ineffective in an in vivo model because this live/dead stain would stain all cells in an animal model in addition to the bacteria. A stain for an in vivo model is required that would allow a distinction between *S. aureus* and the host animal cells. *S. aureus* was added to three osteoblast monolayers cultured on PMMA discs and incubated for two hours. At the two hour point the osteoblast discs were removed from the *S. aureus* medium to stop bacteria invasion and stained with Cell Tracker green, Hexidium Iodide, or a Live/Dead Stain of SYTO 9 and Propidium Iodide. A fourth osteoblast disc prestained with Cell Tracker green was incubated for two hours with Hexidium iodide-prestained *S. aureus*. At the two hour point all osteoblast discs were visualized under the confocal microscope. The osteoblast disc poststained with live/dead stain showed distinct live osteoblast nuclei and cytoplasm with similarly colored live *S. aureus*. The hexidium iodide-poststained osteoblast disc showed distinct nuclei without distinct cytoplasm and indistinguishable bacteria. The cell tracker green pre- and post-stained osteoblast disc did not show distinct nuclei, cytoplasm, or bacteria. None of the current stains would allow a clear distinction between *S. aureus* and osteoblast cells that could be used in an animal model. Further research will use *S. aureus* with a gfp chromosomal insertion that will allow absolute distinction between fluorescent bacterial biofilm infections and live/dead stained osteoblast cells.

ABSTRACT

EVALUATION OF THE RAMP POSITIONER IN OBESE PATIENTS UNDERGOING GASTRIC BYPASS SURGERY

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Sponsored by: Carin A. Hagberg M.D. Department of Anesthesiology

Supported by: University of Texas Health Science Center - Office of the Executive Vice-President for Academic Affairs

University of Texas Medical School at Houston - Office of the Dean

Key Words: RAMP, Cormack-Lehane

Introduction: Airway management of the obese patient requires special consideration, especially regarding patient positioning. The Rapid Airway Management Positioner (RAMP; AirPal, Center Valley, PA) is designed to place the patient into the proper head-elevated laryngoscopy position (HELP). The purpose of this study was to determine if the RAMP is a useful positioning device for direct laryngoscopy and tracheal intubation in obese patients undergoing gastric bypass or laparoscopic gastric banding surgery.

Methodology: Following informed consent, 50 obese patients, ASA I-III, BMI >30 kg/m² were enrolled in the study. General anesthesia was induced with propofol (2-3 mg/kg) and rocuronium (0.6 mg/kg). The anesthesiology resident performed laryngoscopy and the laryngoscopic view was assessed with the patient in the neutral and ramped position. A photograph of both positions was taken by the AirwayCam and graded by an anesthesiologist. Number of attempts at laryngoscopy, ease of ventilation, and external manipulation were recorded.

Results: Patient demographics remained constant in the study since both the flat and ramped positions were compared in the same patient. The ramped position demonstrated an improvement in the Cormack-Lehane grade in 46% of the cases ($p < 0.002$). A total of 23 cases showed improvement, (13 improved by 1, 8 improved by 2, and 2 improved by 3 grades). Additionally, 32% of the cases showed improvement in mask ventilation ($p < 0.01$) in the ramped position.

Conclusion: The RAMP effectively positions obese patients in the ramped position and improves the laryngoscopic view. This device may be useful for difficult to mask ventilate and/or intubate obese patients.

ABSTRACT

The Prevalence of Cardiac Involvement in Pediatric Sarcoma Patients

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Class of 2011

Sponsored by: William I. Douglas, MD, Associate Professor and Chief, Division of Pediatric Cardiovascular Surgery

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

Key Words: Sarcoma, cardiac metastasis, echocardiogram, doxorubicin

Sarcomas are connective tissue cancers that are responsible for 1000-1200 pediatric deaths each year. An IRB approved study was designed to determine 1) the prevalence and the nature of cardiac involvement in pediatric sarcoma patients, 2) the extent of cardiac involvement with specific forms of therapy, namely cardiotoxic chemotherapy in the form of doxorubicin, and 3) the survival characteristics of pediatric patients with pericardial effusion and cardiac metastasis. A comprehensive database was created using the medical records of 516 pediatric patients with a diagnosis of sarcoma between 1997 and 2007 at M.D. Anderson. Cardiac involvement was assessed for the 307 patients with at least one echocardiogram, and the findings of 1330 echocardiograms were quantitatively classified using an ordinal scale. Descriptive statistics have been generated to indicate each patient's maximum degree of cardiac involvement. Left ventricular dysfunction occurred in 116 patients (37.8% of total patients) with 84 (27.4%) experiencing mild dysfunction, 24 (7.8%) moderate dysfunction, and 8 (2.6%) severe dysfunction. 180 patients received cumulative doses of doxorubicin of at least 300 mg/m² and at least 1 echocardiogram. 91 (50.6%) of these patients experienced LV dysfunction compared to 25 (19.7%) of the 127 patients with cumulative doses of doxorubicin less than 300 mg/m² and at least 1 echocardiogram. Furthermore, cardiac metastasis was found in 7 patients (2.4%) with 2 being hemodynamically significant, and pericardial effusion for 18 patients (5.9%). It can be concluded that patients receiving cumulative doses of doxorubicin in excess of 300 mg/m² face an increased risk of cardiac involvement.

Patient Group	Left Ventricle Function			
	Normal	Mild dysfunction	Moderate dysfunction	Severe dysfunction
Patients with known cumulative doses of doxorubicin of more than 300 mg/m ²	49.40%	36.70%	10.60%	3.30%
Patients with unknown or cumulative doses of doxorubicin of less than 300 mg/m ²	80.30%	14.20%	3.90%	0.02%

ABSTRACT

Early Cytokine Response in Hemostatic Resuscitation

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Sponsored by: Ernest A. Gonzalez, MD, Department of Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35
DK007676-15

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

Key Words: Massive Transfusion, Multiple Organ Failure (MOF), cytokine, chemokine

We hypothesized that critically injured trauma patients receiving massive transfusion (MT) who develop Multiple Organ Failure (MOF) will display early differences in patterns of cytokine expression. This study was conducted in the Shock Trauma Intensive Care Unit (STICU) at Memorial Hermann Hospital (Houston, TX). Patients eligible for inclusion were those who met criteria for our 24h standardized resuscitation protocol with evidence of: 1) major torso trauma without severe brain injury (2) hypotension or metabolic stress and 3) required at least one unit of transfused packed red blood cells. From January, 2005 to December, 2006, 48 patients were accepted into the study. Serum samples were collected upon entry and then every 4 hours for the first 24h. Patient demographics were recorded and MOF assessed by the Denver MOF score. Analysis of the cytokine expression was done via Bioplex immunoassay. The traditional predictors of MOF including age, ISS, admission Hg, INR and base deficit were not significantly different between MT-MOF and MT-nonMOF patients. Of the 31 massively transfused patients, 11 (35%) developed MOF. Moreover, patients undergoing MT that developed MOF had significant temporal differences in cytokine expression (Table). The data revealed that early differences in temporal cytokine expression exist in MT patients who developed MOF. Therefore, in the future, this data could allow for the identification and the implementation of novel therapeutic modalities in this cohort of patients.

Temporal Cytokine Expression Post Trauma						
Markers	2-6 Hrs	6-10 Hrs	10-14 Hrs	14-18 Hrs	18-22 Hrs	22-24 Hrs
IL-1ra						
IL-6						
IL-8	X	X	X	X	X	
IL-10		X		X		
Eotaxin				X	X	
G-CSF					X	
GM-CSF			X	X	X	
IFN- γ				X		
TNF- α						
IP-10						
MIP-1b	X			X		



ABSTRACT

Quantification of Epidermal Growth Factor Receptors (EGFR) in SKNAS and SKNSH Cancer Cell Lines

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Sponsored by: Andrew Bean, PhD., Neurobiology and Anatomy
Peter Zage, MD, PhD., Pediatric Oncology, MD Anderson Cancer Center

Supported by: Andrew Bean, PhD
University of Texas Medical School at Houston - Office of the Dean

Key Words: EGFR, neuroblastoma

Background: Neuroblastoma is the most common extracranial solid tumor in children, with approximately 600 new cases occurring each year in the United States. Epidermal growth factor receptors (EGFRs) are aberrantly overexpressed in some neuroblastomas and could underlie the cellular proliferation observed.

Purpose: As part of a larger study on EGFR trafficking we sought to determine the number of EGF receptors on the surface of two neuroblastoma cell lines SKNAS and SKNSH that have reduced EGFR trafficking.

Methodology: HeLa cells (control) were grown in DMEM containing 10% FBS and 1% penicillin-streptomycin. SKNAS and SKNSH cells were grown in RPMI containing 10% FBS, 1% penicillin-streptomycin. Twenty-four hours after plating, cells were washed with 1% PBS and collected by scraping. Supernatant was removed and cells were incubated with EGFR Antibody linked to the fluorophore PE (positive control), Mouse IgG PE (non-specific binding), or no antibody (negative control). Samples were incubated for 1 hour at 4°C in the dark and washed twice with PBS containing 1% BSA prior to FACS analysis. Anti-Mouse IgG beads (Quantum Simple Cellular) were used for quantification of receptors.

Results: Mean fluorescence of samples was obtained using FloJo Software, and receptor number was calculated using QuickCal v2.3 (Bangslabs). Knowing that HeLa cells have significantly more receptors than other cell lines, I determined the optimal amount of antibody required for saturation of all EGFRs on HeLa cells and used the same antibody concentration for the other cell lines. I determined that HeLa cells have 142,000 receptors/cell while SKNAS and SKNSH have 79,900 and 106,100 receptors/cell, respectively.

Conclusions: I developed a method for quantitation of the number of cell surface EGFRs on neuroblastoma cell lines using FACS. This method will be used to examine the hypothesis that tumor suppressor proteins may affect EGFR trafficking resulting in uncontrolled cell growth.

ABSTRACT

The Role of TGF- β and PTHrP in Hepatic Regeneration

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

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16; Tien C. Ko: Studies in gastrointestinal endocrinology, NIH P01-
DK35608 ; University of Texas Medical School at Houston - Office of the Dean

Key Words: Hepatic Regeneration, TGF- β , PTHrP, Partial Hepatectomy

Introduction: Previous studies have implicated the important role of TGF- β signaling pathway in hepatic regeneration after partial hepatectomy (PH). PTHrP, a polypeptide that plays a critical role in cellular proliferation, differentiation and apoptosis, has been identified as a downstream target of the TGF- β signaling pathway in *in vitro* model. We hypothesize that the TGF- β signaling pathway interacts with the PTHrP signaling pathway during hepatic regeneration.

Methods: 70 Swiss Webster mice were divided into two groups: sham with laparotomy as control and 70% partial hepatectomy. Mice were sacrificed at 2, 6, 12, 24, 48, 72 h and 7 d (n=5), and liver tissues and serum samples were collected. Hepatic regeneration was determined by hepatic weight/total body weight and proliferating cell nuclear antigen (PCNA) staining. Levels of TGF- β 1 and PTHrP mRNA expression were determined by quantitative real-time PCR. TGF- β 1 protein levels were measured using an Enzyme-Linked ImmunoSorbent Assay (ELISA). PTHrP protein expression was examined by Western Blot Analysis.

Results: Hepatic regeneration was initiated at 12 h post-hepatectomy and restored to 72% of the original mass compared to sham by day 7. PCNA positive cells were 42.8 \pm 5.6 in the hepatectomy group compared to 0.6 \pm 0.6 in the sham group per 20X field at 72 h. TGF- β 1 mRNA expression increased at 6, 12, 24 and 48 h post-hepatectomy compared to the sham group. TGF- β 1 serum protein increased at 24 h post-hepatectomy compared to the sham group. PTHrP mRNA expression decreased at 6 h and increased at 24 h post-hepatectomy compared to sham.

Conclusions: Both TGF- β 1 and PTHrP expression are up-regulated at several time points during the process of hepatic regeneration, demonstrating their involvement in hepatic regeneration. The increase in TGF- β 1 precedes the induction of PTHrP, suggesting that TGF- β 1 acts upstream of PTHrP during hepatic regeneration. Further study is necessary to better understand the roles and interaction of TGF- β and PTHrP in hepatic regeneration.

ABSTRACT

Investigation of Mechanical Stress as a Stimulus of Intestinal Dysfunction in Gut Edema

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

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35
DK007676-15

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

Key Words: Edema, intestines, mechanotransduction

Intestinal edema is a common result of damage control laparotomies and fluid resuscitation in trauma patients, which often leads to intra-abdominal hypertension and subsequent abdominal compartment syndrome. Past investigations have linked gut-edema to ileus, demonstration a decrease in contractility and delayed intestinal transit in rat models. It has been suspected that gut edema acts through a mechanotransductive pathway that leads to intestinal dysfunction, as there have been numerous molecular alterations with edema suggestive of this hypotheses. Intestinal edema has been shown to increase STAT3 activation and decrease myosin light chain (MLC) phosphorylation. Decreased stiffness and residual stress of the small intestine has also been apparent with edema, measured using the elastic modulus and opening angle, respectively. Stress fiber formation was additionally demonstrated, as indicated by increased F:G Actin ratios in edematous rat models.

A rat model was created in order to test the mechanotransductive hypothesis of gut edema in which rat ileum was stressed longitudinally and circumferentially for a period of two hours at an equivalent pressure to that of edematous interstitium. Tissue was harvested from sixteen rats and analyzed for nuclear STAT3 activation, STAT3 phosphorylation, and MLC phosphorylation. Using the secant modulus of a stress-strain profile of the intestinal tissue, the elastic modulus of the intestine was also evaluated in an additional circumferential stretch group of rats. A one tailed t-test showed a significant increase in STAT3 activation in the mucosa of the intestine, an increase in STAT3 phosphorylation in seromuscular and mucosal layers, and a decrease in MLC phosphorylation in both intestinal layers of the stressed tissues. The elastic modulus evaluation showed a significant increase in tissue stiffness following stretch. While the modulus findings yield conflicting results and further investigation must be taken to determine its significance, the molecular markers who a consistent pattern with past studies of intestinal edema. These results are further supportive of a mechanotransductive link between the action of edema and intestinal dysfunction as isolated mechanical stress produced similar molecular events.

ABSTRACT

Evoked Potentials and Myoglobinemia following Aortic Repair

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Sponsored by: Charles C. Miller, III, Ph.D., Department of Cardiothoracic and Vascular Surgery

Supported by: Charles C. Miller, III, Ph.D., Department of Cardiothoracic and Vascular Surgery ; University of Texas Medical School at Houston – Office of the Dean

Key Words: Thoracoabdominal Aortic Aneurysm Repair, Myoglobin, Motor and Somatosensory Evoked Potentials, Kidney Dysfunction

Background:

We have previously demonstrated that the risk of renal dysfunction associated with thoracoabdominal aortic repair can be predicted by monitoring the course of serum myoglobin levels during the first three postoperative days. Separately, we have also shown that somatosensory evoked potentials are a practical intraoperative tool in predicting postoperative renal failure. In this study we describe the relationship between evoked potential signal changes and the postoperative course of serum myoglobin as these relate to postoperative renal failure following DTAA and TAAA repair.

Methods:

We performed a retrospective chart review, which provided somatosensory and motor evoked potential data as well as serum myoglobin data three days postoperative, of 146 patients who had undergone descending or thoracoabdominal aortic repair between September 2006 and March 2008. Renal failure was defined according to the RIFLE criteria (the need for hemodialysis or the postoperative doubling of baseline creatinine levels).

Results:

MEP data was classified as no change (62/146; (43%)), temporary change (75/146; (51%)), or permanent change (7/146; (4.7%)) and uninterpretable (2/146; (1.3%)). SSEP data was classified as no change (100/146; (68.5%)) or change (46/146; (31.5%)), which included both temporary and permanent changes. Serum myoglobin data was not complete for all patients three days postoperative. A permanent change in MEPs or any change in SSEPs were strong predictors of the course of postoperative serum myoglobin levels.

Conclusions:

A compelling relationship exists between a permanent change in MEP or any change in SSEP and an elevation in postoperative serum myoglobin levels. While these two indicators did not correlate in a statistically significant fashion to renal failure, there is a convincing trend between intraoperative changes in evoked potentials, postoperative serum myoglobin levels and concomitant renal failure.

ABSTRACT

Effect of a Web-Based Presentation on Communication with Healthcare Providers

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Sponsored by: Kevin O. Hwang, MD, Department of Internal Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35 DK007676-16 ; University of Texas Medical School at Houston - Office of the Dean

Key Words: Obesity, Berlin Questionnaire, Sleep Apnea

PURPOSE: Obstructive sleep apnea (OSA) is common among obese individuals and is frequently undiagnosed. Effective ways to improve OSA diagnosis among obese individuals are needed. Therefore, we conducted a pilot randomized trial of a web-based OSA awareness campaign among members of an online weight loss community (SparkPeople.com) to encourage high-risk individuals to talk to their healthcare providers (HP) about OSA.

METHODS: Members of SparkPeople.com who have never discussed OSA with their HP were randomized to usual care (nothing) or intervention. The intervention group took the Berlin Questionnaire (BQ) to assess OSA risk. High-risk subjects were sent a web-based presentation about OSA, encouraging them to talk to their HP. Low-risk subjects were sent a web-based report of their results. At 3 months, all subjects will be asked about the outcome of their contact with their HP.

RESULTS: A total of 168 individuals were randomized to intervention (n=84) or usual care (n=84). Subjects were mostly female [163/168 (97%)] and Caucasian [152/168 (90.5%)], with mean age $39.5 \pm SD 11.7$ and mean body mass index $30.3 \pm SD 7.8$. Of the 84 in the intervention group, 82 took the BQ and were identified as high-risk [32/82 (39%)] or low-risk [50/82 (61%)] for OSA. To date, 30/32 (93.8%) high-risk and 49/50 (98.0%) low-risk subjects have viewed their respective presentations. Three month assessment data are pending.

CONCLUSION: This OSA online awareness campaign was feasible. Analysis of results will yield information on the campaign's effectiveness in encouraging high-risk individuals to talk to their HP about OSA.

ABSTRACT

Detection of Viral Shedding of VZV Oka Strain (in Saliva and at the Vaccination Site) of Patients Post-ZOSTAVAX Administration

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

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35 DK007676-16

Key Words: VZV, shingles, ZOSTAVAX®, vaccine

The purpose of this study was to determine if Varicella- Zoster Virus (VZV) DNA can be detected by Polymerase Chain Reaction (PCR) from the saliva and at the inoculation site of patients who have been injected with live attenuated varicella-zoster vaccine for the prevention of herpes zoster. It was hypothesized that VZV DNA will be found in samples of saliva and at the post-inoculation site after vaccination. If it is found that detectable amounts of VZV DNA are present in the samples, there may be increased risk for transmission of the virus to susceptible populations. Non-immunocompromised patients were identified as eligible recipients of the VZV vaccine. Pre-vaccination samples from the saliva served as controls for the presence of VZV. The vaccine was administered subcutaneously. Post-vaccination samples were obtained 5 minutes post vaccination at the inoculation site, and of the saliva at regular time intervals after vaccination: 5 minutes; 1 day; 7 days; 14 days; and 28 days. Real time PCR was performed on the samples to detect the presence of VZV virus (Oka strain) DNA. Post inoculation samples will be compared to pre-inoculation control samples to determine if there is significant 'shedding' of the virus after vaccination. Results of the real time PCR will be reported once they are obtained.

ABSTRACT

Quantitative PCR for Varicella-zoster Virus DNA in Multiple Sclerosis

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Sponsored by: John W. Lindsey, MD, Department of Neurology

Supported by: John W. Lindsey, MD, Department of Neurology

University of Texas Medical School at Houston - Office of the Dean

Key Words: Multiple Sclerosis, Varicella-zoster, qPCR, ORF31

Varicella-zoster virus (VZV) has been associated with Multiple Sclerosis (MS) although there are no definitive implications for the role of VZV in MS patients as of yet. We hypothesized that the reactivation of VZV might be responsible for the immune response and subsequent symptoms in relapsing cases of MS. Blood samples were collected from MS patients at time of relapse and stable conditions and matched to controls. Quantitative PCR (qPCR) was used to determine the amounts of VZV DNA present in the peripheral blood leukocytes (PBLs) of each sample by amplifying a 110 base pair amplicon of the ORF 31 gene present in VZV. Our results of eight MS patients tested yielded three with undetectable levels of VZV DNA at both relapse and stable conditions. While two patients did have higher levels of VZV DNA present at relapse, three other patients had lower levels of DNA at relapse. In addition, four of the matched controls had measurable levels of VZV DNA. Given the results no significant correlation can be made between the activity of VZV and patients with more active MS compared to stable patients or controls. We conclude that it is unclear if VZV plays any role in the pathogenesis of MS.

ABSTRACT

Role of Oxidative Stress in Irradiated Rats

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

Supported by: Marie Françoise Doursout, PhD

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

Key Words: Radiation, Reactive Oxygen Species(ROS), Nitric Oxide

Potential exposure to life-threatening radiation sources is a critical problem that presently impacts humans involved in space exploration, work at nuclear energy reactor facilities and soldiers engaged in military activities where the potential for nuclear attack is high. Depending on the source and level of exposure, clinical implications can include cancer, accelerated cardiovascular disease, depleted immunity, and acute radiation syndromes (Townsend Lawrence (2005). Recent studies using low doses of ionizing radiation (Kennedy et al (2004) reported the involvement of reactive oxygen species (ROS) or reactive nitrogen species (RNS) that transiently activate nitric oxide synthase (Leach et al. (2002). Therefore, the goal of this study is to assess the role of the NO-sGMP pathway on radiation exposure in conscious rats. Five control rats and five treated rats were used in this study. Treated rats were subjected to radiation exposure at 2Gy for 20 min (dose rate 0.1 Gy/min) using a Nordian Gammacell 40 Exactor Irradiator. Animals were sacrificed 3 hr following irradiation. Tissues (heart, lung, kidney, liver, gut and skin) were harvested and maintained at -70° for further chemical assays. Western blots analysis and protein content were performed on collected tissues. Western blot analysis of lung and kidney tissue demonstrated a rapid decline of protein levels of SGC alpha1 and beta1 subunits. This data indicates that oxidative stress selectively degrades SGC protein. This causes systemic dysregulation of the NO-sGMP pathway. Our findings will help to weigh the risks of a radiation exposure and anticipate its damaging consequences for human cardiovascular health.

ABSTRACT

An *In-vitro* Model for Intestinal Edema

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Sponsored by: Karen S. Uray, Ph.D., Department of Pediatric Surgery

Supported by: NIH grant DK56338, which supports the Texas Medical Center Digestive Diseases Center

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

Key Words: STAT3, ileus, intestinal edema, smooth muscle

Resuscitation induced intestinal dysfunction often develops in traumatically injured patients and leads to increased morbidity and prolonged hospital stays resulting in an estimated \$750 million in annual health care costs in the United States. Specifically, damage-control surgical techniques of intra-abdominal packing and fluid resuscitation alter Starling forces promoting interstitial, intestinal edema (increased capillary pressure and decreased plasma oncotic pressure). It has been demonstrated that intestinal edema causes ileus as measured by decreased intestinal transit and depressed smooth muscle contractility. Edema-induced ileus is at least partially mediated by increased STAT3 signaling. We developed an *in-vitro* model to test the effects of edema-associated pressure changes on human intestinal smooth muscle cells, and we developed a protocol for immediate cell collection to prevent degradative enzymatic activity. Human intestinal smooth muscle cells were grown on a flexible membrane and then subjected to cyclical vacuum stress, deforming the membrane. Cells were then rapidly frozen and collected. Two programs were used to regulate vacuum stress on the membrane: (1) a control program that modeled the cyclical changes in stress associated with normal gut activity and (2) a program of increasing cyclic stress on the membrane to mimic conditions of intestinal edema. We have measured increased STAT3 and NF-kappaB DNA binding activity and decreased rho kinase activity in the edema model versus the control model; these results are similar to animal models of interstitial, intestinal edema indicating that this *in-vitro* model will be useful for future studies of interstitial edema.

ABSTRACT

Morphoproteomic characterization of signal transduction pathways in adult CD133+ stem cells derived from human bone marrow

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Sponsored by: Robert Brown, MD, Department of Pathology

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

Key Words: Morphoproteomic, Lymphocytoid, Cytopsin

Bone marrow-derived stem cells have the potential for regenerative medicine. However, there are also data to implicate bone marrow-derived stem cells in the origin of epithelial cancers. This study was designed to characterize the signal transduction pathways in bone marrow-derived stem cells in order to gain a better understanding of their biology. CD133+ cells, the putative primitive stem cells, were isolated from the peripheral blood of normal donors and from a culture of commercially obtained bone marrow-derived stem cells. CD133+ expression was confirmed by flow cytometric analysis of these enriched populations. Probes were applied to cytopsin preparations to detect certain protein analytes and peripheral blood mononuclear cells (PBMCs) depleted of CD133+ cells were concurrently evaluated, serving as a control. The chromogenic signal (staining intensity) and the cellular compartmentalization of the signal (plasmalemmal, cytoplasmic and/or nuclear) were evaluated by bright field microscopy and scored on a scale of 0-3+. CD133+ cells from bone marrow and peripheral blood showed moderate to strong nuclear and plasmalemmal reactivity for p-Akt, p-mTOR, p-p70S6K, p-ERK 1/2 and p-NF-kappaBp65 and with evidence of intracellular trafficking (i.e. cytoplasmic reactivity in some cells and combined with nuclear reactivity in others). Contrastively, the overall staining pattern in PBMCs was either less in the case of p-Akt, p-mTOR and p-p70S6K or confined to a specific cellular subtype such as lymphocytoid and monocytoid cells. In summary, morphoproteomic analysis identifies constitutive pathways of convergence in adult CD133+ stem cells derived from human bone marrow, serving as a framework for improved therapeutic intervention.

ABSTRACT

Use of Mesenchymal Stem Cells to Enhance Hippocampal Neurogenesis Following Traumatic Brain Injury

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16

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

Key Words: hippocampus, MSCs, neurogenesis, brain injury

Previously, it has been reported that stem cells derived from bone marrow could be used to improve neurobehavioral outcomes following traumatic brain injury (TBI). However, the cellular and molecular mechanisms by which this improvement is achieved is unknown. Wnt-mediated signaling has been demonstrated to be obligatory for hippocampal neurogenesis in the adult brain. Using bone marrow-derived stem cells, we tested the *hypothesis* that stem cells expressing Wnt3a will increase endogenous hippocampal neurogenesis in TBI animals. First we tested if bone marrow-derived mesenchymal stem cells (MSCs) by themselves or MSCs modified to express Wnt3a protein can increase neurogenesis in uninjured animals. MSCs, MSCs transfected with a plasmid expressing the Wnt3a protein, or saline (as an alternate vehicle) were unilaterally injected into the hippocampus. Beginning 24 hours after cell transplant, animals were injected with 50mg/kg bromodeoxyuridine (BrdU) in order to detect newly-divided neurons. Twenty-four hours after the second BrdU injection, the rats were perfused and neuronal tissues were fixed in paraformaldehyde. The tissue was then sectioned using a Cryostat machine and these slices were stained with a BrdU-antibody. The number of BrdU-positive cells was counted to estimate the number of new neurons formed. Following the completion of cell counting, the blind code will be broken and animals grouped for statistical comparison. Results from this study are currently being obtained. My prediction is that bone marrow-derived mesenchymal stem cells (MSCs) will increase neurogenesis, and that the Wnt protein will increase this rate even further.

ABSTRACT

Exploring the Regulation of TRPV Channels by Nitric Oxide

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Class of 2011

Sponsored by: Roger G. O'Neil, PHD, Department of Integrative Biology & Pharmacology

Supported by: National Institute of Health, NIDDKD 2 T35 DK007676-16 and NIDDKD R01 DK 070950 (to R.G. O'Neil)

University of Texas Medical School at Houston - Office of the Dean

Key Words: TRPV, nitric oxide

Transient receptor potential (TRP) channels are a relatively new class of calcium-permeable channels expressed in tissues such as the kidney and brain. Recent studies suggest that nitric oxide (NO) can activate selected TRP channels either directly via nitrosylation of the channel or indirectly through the guanylyl cyclase/protein kinase G signaling cascade. This study is designed to investigate how NO regulates calcium influx through TRPV2/4, TRP channels belonging to the vanilloid subfamily.

Mouse renal (M-1) cells endogenously expressing TRPV2 and TRPV4 channels were grown on coverslips. Fura-2 (a calcium-sensitive probe) fluorescence imaging was used to measure intracellular calcium concentrations. After being bathed in isotonic MBSS buffer, M-1 cells were incubated with various combinations of either 100 μ M SNAP (NO donor), 10 μ M ruthenium red (TRPV inhibitor), 1 μ M ODQ (guanylyl cyclase inhibitor), or 100 μ M 8-Br-cGMP (cGMP analog). Applying each agent independently, both SNAP and ODQ elicited significant calcium influxes which were abolished when the cells were first incubated with ruthenium red. This suggests that NO is specifically activating TRPV2 or TRPV4 and that the guanylyl cyclase product, cGMP, is constitutively inhibiting either channel. Application of 8-Br-cGMP did not elicit a calcium influx by itself, but it did reduce the calcium influxes elicited by both SNAP and ODQ, indicating that cGMP may inhibit TRPV2 or TRPV4 activity.

In conclusion, our data shows that NO activates TRPV2 or TRPV4, potentially by direct nitrosylation, while the guanylyl cyclase signaling cascade inhibits TRPV2 or TRPV4. Future studies involving cell lines expressing only TRPV2 or TRPV4 will help elucidate whether TRPV2, TRPV4, or both are responsive to NO and the guanylyl cyclase pathway.

ABSTRACT

Mechanism of Glutamine's Effect on Peroxisome Proliferator-Activated Receptor- γ

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Sponsored by: Rosemary A. Kozar, M.D., Ph.D., Department of Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases,
5T35 DK007676-15

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

Key Words: Glutamine, PPAR γ , PPRE, ligand

Introduction: Gut protection under conditions of oxidant stress is mediated in part by the anti-inflammatory transcriptional regulator, peroxisome proliferator-activated receptor-gamma (PPAR γ). PPAR γ possesses both ligand dependent and independent mechanisms of binding. We have demonstrated that glutamine activates PPAR γ via an indirect ligand dependent mechanism. 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂ (15d-PGJ₂) is a product of arachidonic acid metabolism and the most potent natural, endogenous ligand for PPAR γ identified to date. Therefore, we hypothesized that 15d-PGJ₂ would be the ligand mediating glutamine-induced activation of PPAR γ .

Methods: Intestinal epithelial cells (IEC-6) were pretreated with increasing concentrations of glutamine (0 – 10 mM), and then cultured medium and cell lysates were analyzed by ELISA for 15d-PGJ₂ concentration. The upstream mediators of arachidonic acid metabolism, COX-1 and COX-2, were measured by Western Blot. The products of glutamine metabolism, glutamate and glutathione, were analyzed by EMSA to investigate the level of PPAR γ activity. Lastly, potential ligands of the lipooxygenase pathway were screened by liquid chromatography/tandem mass spectroscopy (LC/MS/MS).

Results: There was an inverse correlation observed between 15d-PGJ₂ and glutamine concentrations and no change in the enzyme expression levels of COX-1 or COX-2. Similarly, there was no change in PPAR γ activity by glutamate or glutathione concentrations as a function of glutamine. Preliminary results from LC/MS/MS suggest that concentrations of 15-HETE, 13-HODE and 13-OXO of the LOX pathway increase with increasing glutamine concentration.

Conclusion: Though glutamine activates PPAR γ by an indirect ligand dependent mechanism, the actual ligand remains unclear. The potential ligands involved in the LOX pathway will be further investigated to determine their potential role in gut protection via PPAR γ activation.

ABSTRACT

In Situ Structure and Mechanism of Spirochete Flagella Revealed by Cryoelectron Tomography

ERIN C. MCCRUM

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Sponsored by: Jun Liu, PhD
Department of Pathology

Supported by: Dr. Liu and the Department of Pathology
University of Texas Medical School at Houston – Office of the Dean

Key Words: Cryo-EM, Lyme Disease, flagella, mutant, *Borrelia burgdorferi*

Borrelia burgdorferi causes the most common vector borne disease in the United States- Lyme disease. Flagella motility is a vital component of *Borrelia burgdorferi* pathogenesis, allowing the bacteria to exit the bloodstream, invade tissues, and evade the host immune response. Each of *Borrelia*'s flagella is powered by a 'motor' located in the inner membrane that is composed of more than 20 proteins. Although flagella motors have been actively investigated for more than half a century, the structure and function of these biological machines remains the subject of academic debate. Understanding *Borrelia*'s motor structure and mechanism is impractical using routine techniques. Light microscopy lacks sufficient resolution. X-ray crystallography is not an imaging technique that allows visualization of the intact motor structure, and biochemical techniques simply can not provide in-depth structural detail. Using Cryo-electron tomography (Cryo-ET) and 3-D averaging, we compared both gross cellular morphology and sub-cellular flagella motors of wild-type *Borrelia burgdorferi* with a *Borrelia burgdorferi* P-ring motor mutant. In doing so, we demonstrate that not only is the P-ring important for the formation of intact flagella, but that Cryo-ET is a new and powerful tool in the arsenal of genetic analysis, capable of simultaneous examination of both molecular structure and overall organism morphology.

ABSTRACT

Promising Evidence of Vitamin D induced Protection Against Oxidative Damage in THP-1 Macrophages

DAVID MCMANN

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Sponsored by: Chinnaswamy Jagannath, Ph.D.

Supported by: A Grant from The NIH.

Key Words: Vitamin D3, Macrophage, Oxidative Damage

Vitamin D3 is emerging as a major mediator of innate immunity and protection against infection and tumor formation. Oxidant mediated damage to cells is also a major mechanism of cell death which is accelerated during aging. In order to determine if Vitamin D₃ protected against cellular damage due to oxidative stress, we investigated the effects of Vitamin D₃ on the viability of human macrophages facing an oxidative challenge using hydrogen peroxide. **METHODS:** THP-1 monocytes were first activated with Vitamin D₃ (concentrations from 10⁻⁵ M to 10⁻⁷ M) followed after three days by a treatment of 0.1% Hydrogen peroxide (H₂O₂). The THPs were then stained for viability using both Calcein AM and Ethidium homodimer fluorogenic reagents and submitted to flow cytometric analysis using a Cellquest software and BCD Facscan. These fluorescent stains discriminate between live and dead cells during flow cytometry. **RESULTS:** A dose of 0.1% of H₂O₂ was found to be lethal to THP-1 macrophages. THPs treated with 10⁻⁵ M Vitamin D₃ however showed increased viability demonstrating protection against the oxidative damage induced by H₂O₂. This finding was reproducible and suggests that VitaminD3 can be used to prevent oxidant mediated damage to healthy cells.

ABSTRACT

Familial Thoracic Aortic Aneurysms and Dissections: A Subset of Families with Thoracic Aortic Aneurysms in Men and Intracranial Aneurysms in Women

SARAH K. MEDREK *The University of Texas at Houston Medical School* *Class of 2011*

Sponsored by: Dianna M. Milewicz, MD, Department of Internal Medicine, Department of Medical Genetics

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

Key Words: Thoracic aortic aneurysm, intracranial aneurysm

Thoracic aortic aneurysms leading to type A dissections are usually inherited as an autosomal dominant condition with variable expression and decreased penetrance (FTAAD). Genetic heterogeneity for FTAAD is established and correlates with clinical heterogeneity. For example, FTAAD resulting from TGFBR1 or TGFBR2 mutations is associated with aneurysms and dissections of other arteries, including fusiform intracranial aneurysms. In our cohort of 450 families with FTAAD, we noted that approximately 10% of families had one or more members with intracranial berry aneurysms (ICA), in contrast to the fusiform aneurysms associated with TGFBR1/2 mutations. In three large families, women with ICAs were confirmed to harbor the defective gene causing TAAD based on their location in the pedigree. Interestingly, males in these families tended to have TAAD and females tended to have ICA. Linkage analysis with DNA from the largest family with 12 affected members indicated that the phenotype was not linked to any of the known TAAD loci and no TGFBR1/2 mutations were identified, indicating that the subphenotype of TAAD/ICA is caused by a novel gene. Imaging of both the thoracic aortic and intracranial arteries is recommended in these families. Detection of a novel gene would increase the mechanistic and clinical understanding of both TAAD and ICA.

ABSTRACT

Mechanisms of Fat Storage in Obesity: Exploring the roles of S3-12 and Perilipin in Fat Packaging and Storage

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Sponsored by: Perry E. Bickel, MD, Center for Diabetes and Obesity Research, Brown Foundation Institute of Molecular Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35 DK007676-16
University of Texas Medical School at Houston – Office of the Dean

Key Words: S3-12, perilipin, lipid droplet, adipocyte

S3-12 and perilipin are lipid droplet binding proteins expressed primarily in adipocytes. Whereas S3-12 associates with new lipid droplets during rapid triacylglycerol synthesis, perilipin constitutively associates with a distinct population of lipid storage droplets. The purpose of this study was to determine whether S3-12 and perilipin functionally interact to promote fat storage. The purpose was to also see if the intracellular localization of these coat proteins is an intrinsic property of S3-12 and perilipin or if the cyto-architecture is due to an adipocyte cellular process. I hypothesize that triacylglycerol accumulation will be synergistically augmented when both S3-12 and perilipin are expressed as compared to expression of perilipin or S3-12 alone. These aims were tested using HeLa cells, a non-adipocyte cell line engineered to express S3-12 when induced with doxycycline. HeLa cells were transfected with perilipin or control plasmid. Thus, four groups of HeLa cells were created; with or without S3-12 expression and with or without perilipin expression. Each of the four groups was incubated for 24 hours with or without 1.0 mM oleate. HeLa cells were then fixed to slides. S3-12 and perilipin expression and localization were detected via immunocytochemistry and fluorescence microscopy. We noted co-expression of oleate and perilipin in cells suggesting successful transfection. Preliminary data showed that perilipin and S3-12 did segregate, for the most part, onto separate lipid droplets, as in adipocytes, suggesting the HeLa model is an appropriate system for further functional characterization of these proteins.

ABSTRACT

FOXP3 Expression as a Measure of Regulatory T Lymphocyte Numbers in Thermochemotherapy Cancer-Cured Rats

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Sponsored by: Joan Bull, MD, Department of Internal Medicine

Supported by: Joan Bull, MD

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

Key Words: FOXP3, Treg, thermochemotherapy, PBMC, Q-RT-PCR

Regulatory T (Treg) lymphocytes play an essential role in the maintenance of peripheral tolerance. They express the forkhead/winged helix transcription factor FOXP3, which is responsible for Treg development, maintenance, and function. In many types of cancer, their presence is associated with a dampened antitumor response and a clinically worse prognosis. We investigated the activity of Tregs, as measured by FOXP3 mRNA expression, over time in three sets of rats: 1) cancer-cured rats re-challenged with the same aggressive mammary (MTLn3) carcinoma, 2) naïve rats challenged with MTLn3 cells, and 3) naïve age-matched controls. We had previously observed tumor cell rejection upon rechallenge among the cured rats, suggesting an increase in effector function of CD8+ memory and cytotoxic T lymphocytes due to either an increase in CD8+ memory T cells or a decrease in Tregs. Hence, we hypothesized that less FOXP3, a marker for Tregs, would be detected in the cured rats permitting a strong immune response compared to the naïve challenged rats. FOXP3 expression was analyzed by quantitative reverse transcriptase polymerase chain reaction (Q-RT-PCR). Contrary to expectations, preliminary results suggested that naïve challenged rats had no significant difference in FOXP3 expression compared to cured animals. If confirmed, these results suggest that Treg downregulation is not an important part of the antitumor memory response in this model. However, even with our PCR based assay, FOXP3 signals were low, and combined with the lack of a standard curve to validate the data at the high cycle numbers required, absolute quantification was difficult.

ABSTRACT

Mutagenesis of MreB to search for morphogenic variants of *E. coli* with an altered MreB

Auston Myers

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Sponsored by: William Margolin, PhD Department of Microbiology

Supported by:

Key Words: *E. Coli* ; Morphogenic

Objectives: We set out to induce mutations in the *mreB* gene of *Escherichia coli* to search for morphogenic variants of *Escherichia coli* with an altered MreB.

Methods: In order to form altered morphologies of the cells, the native *mreB* gene needed to be inactivated. Thus, we used the strain, WM1579 *mreB11*, that grows with a spherical morphology, suggesting an altered *mreBCD* operon. We then transformed plasmids from three different strains expressing the *mreBCD* operon into *mreB11*. Once the rod shape of the transformed *E. coli* was restored, the plasmid was mutagenized using mutagenic PCR. The mutagenized plasmids were then re-transformed into *mreB11*, and each transformant was viewed for morphological defects microscopically.

Results: The *mreB11* cells transformed with the native *mreBCD* returned to their rod morphology. This indicates that the *mreB11* strain has a mutation in its *mreBCD* operon. The *mreB11* with the mutagenized *mreB* plasmid was never viewed microscopically due to mutagenic PCR complications and time constraints.

Conclusion: We conclude that the WM1579 *mreB11* strain grows spherically most likely due to a mutation in the *mreBCD* gene. This was shown when the *mreBCD* plasmid was transformed into the *mreB11* spherical cells, and the rod morphology was restored. The next step will be to sequence the *mreBCD* genes in the WM1579 *mreB11* strain. Morphogenic variants produced by mutagenic PCR were inconclusive. Further attempts to mutagenize the transformed plasmid in the *mreB11* cells in order to view for altered morphologies are warranted.

ABSTRACT

Differential Advate and Kogenate electrophilic FVIII reactivity to hemophilia A anti-FVIII IgGs

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Sponsored by: Sudhir Paul, PhD Chemical Immunology Department of Pathology

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

Key Words Hemophilia A, anti-FVIII IgG, electrophilic FVIII, irreversible inactivation

The antigen-binding sites of antibodies (Abs) can express enzyme-like nucleophiles that react covalently with electrophilic compounds. Recently, we reported the irreversible and specific reactivity of the electrophilic analog of Factor VIII (E-FVIII) with anti-FVIII inhibitor Abs, that are responsible for failure of FVIII replacement therapy in hemophilia A (HA) patients. E-FVIII contains randomly distributed strong electrophilic phosphonate on its Lys side chains of diverse antigenic epitopes. E-FVIII can form complexes with Abs that are resistant to SDS treatment and boiling, procedures known to dissociate noncovalent

Ab-antigen interactions. Here, we present the development of a new assay to study the covalent interaction of Abs with E-FVIII and compare the reactivity of a panel of HA subjects IgG with E-FVIII synthesized from two commercially available recombinant FVIII formulations, Kogenate and Advate (E-Kogenate and E-Advate).

Methodology: IgGs from HA patients (n=8) were affinity purified on Protein G columns. Irreversible reactions of the IgGs incubated for 20 h with immobilized E-Kogenate and E-Advate were quantified by ELISA. The immune complexes were washed with neutral buffer and then subjected to SDS treatment and boiling before detection of bound IgG.

Results: HA IgGs formed immune resistant to SDS and boiling with E-Advate at levels superior than E-Kogenate. **Conclusion:** The data suggest that the electrophiles in E-Advate are more accessible and better positioned within the noncovalently recognized FVIII epitopes to react with HA IgGs, allowing formation of covalent immune complexes. E-Advate, therefore, is superior to E-FVIII for inactivation of anti-FVIII inhibitor Abs from HA patients.

ABSTRACT

Inhibition of I κ B α Phosphorylation Attenuates LPS-induced Hepatic Injury

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16; NIGMS P50 GM38529
University of Texas Medical School at Houston – Office of the Dean

Key Words: Lipopolysaccharide, aspartate aminotransferase, NF κ B, I κ B α , Genistein

INTRO: Lipopolysaccharide (LPS) causes hepatic injury that may involve enhanced NF κ B transcription factor activity and subsequent changes in expression of oxidative stress proteins such as inducible nitric oxide synthase (iNOS) and cyclo-oxygenase-2 (COX2). Translocation of inactive NF κ B from the cytosol to the nucleus is prevented by the inhibitory protein I κ B α . Inactivation of I κ B α , and subsequent activation of NF κ B usually requires serine phosphorylation of I κ B α . However, an alternative pathway also exists with tyrosine phosphorylation of I κ B α . The aim of this study was to examine the role of I κ B α phosphorylation and NF κ B in LPS-induced hepatic injury. We hypothesized that inhibition of I κ B α phosphorylation would diminish hepatic injury from LPS.

METHODS: Male Sprague-Dawley received Genistein (10 mg/kg IP), an inhibitor of I κ B α tyrosine phosphorylation, or vehicle (DMSO) 1 hour before receiving saline or LPS (20 mg/kg IP) for 5 hours. Serum was collected to measure AST as an index of hepatic injury. Liver was assessed for NF κ B activity (EMSA), iNOS, and COX2 (Western blot) protein immunoreactivity ($n > 5$ /group; ANOVA).

RESULTS: LPS significantly increased AST levels, decreased I κ B α , enhanced NF κ B activity, and upregulated both iNOS and COX2 when compared to controls. In contrast, Genistein attenuated LPS-induced hepatic injury when compared to LPS controls.

CONCLUSIONS: These data indicate that LPS-induced hepatic injury is mediated in part by tyrosine phosphorylation of I κ B α , inactivating it such that NF κ B transcription factor activity is increased, enabling upregulation of oxidative stress proteins.

ABSTRACT

Clavicle Shortening: A New Method of Measurement

ELLIOT ROW *The University of Texas at Houston Medical School*

Class of 2011

Sponsored by: Milan Sen, MD, The Department of Orthopaedic Surgery

Supported by: Milan Sen, MD, Catherine Ambrose, PhD, Kyle Dickson, MD, Manickam Kumaravel, M.D. University of Texas Medical School at Houston - Office of the Dean

Key Words: Clavicle Shortening, chest x-ray, malunion, non union, clavicle fracture

Clavicle fractures are common injuries. In some cases, the two ends of the fractured clavicle will re unite in a way that causes overlap, or shortening of the clavicle. Impairments have been associated with clavicle shortening. The purpose of this study is to determine a more accurate way for measuring clavicle shortening on a chest x ray following clavicle fracture malunion. The first part of the study involved taking shortening measurements from chest x-rays using the previously common method of subtracting the length of the fractured clavicle from the length of the contralateral intact clavicle. These measurements were then compared to the chest CT as a standard. A newer method involved measuring the length of the medial bone fragment, lateral bone fragment and the length of the entire fractured clavicle. The sum of the lateral fragment and medial fragment were then subtracted from the entire length to give the region of overlap. The second part of the study was an analysis of thirty normal chest x-rays to determine if clavicle shortening existed using the old method. We found 22.5% of intact clavicles have differences between right and left larger than 10mm. Reasons for this difference could include unusual sigmoid shape of the clavicle, difficult patient positioning, variable film focus distance, and resultant magnification discrepancies. There were 13% of cases where the difference between the new method and CT value was greater than 10mm compared to the old method which had 47.8% of the cases where the difference between the x-ray and CT is greater than 10mm. These results suggest the new technique is more accurate than the old way of measuring clavicle shortening.

ABSTRACT

Testing the Role of the Cap Proteins in Assembly and Function of the RNA Processing Exosome

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Sponsored by: Ambro van Hoof, PhD, Department of Microbiology and Molecular Genetics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35
DK007676-15
University of Texas Medical School at Houston – Office of the Dean

Key Words: Exosome, Rrp4p, Rrp40p, RPL27, S1, KH

The exosome is an exoribonuclease complex with roles in mRNA degradation, RNA processing and anti-viral defense. The exosome includes six proteins that form a ring structure and three that cap the ring. It has been proposed that the cap proteins are important for exosome assembly by bridging interactions between the ring subunits. Two of these cap proteins, Rrp4p and Rrp40p each contain three domains: RPL27, S1 and KH. We have tested whether each of these domains have specific functional or structural roles, or whether a domain from one of the proteins can substitute for the paralogous domain. Six chimeric proteins of Rrp4p and Rrp40p were created and introduced into *Saccharomyces cerevisiae* strains that contained deletions of the RRP4 or RRP40 genes. None of the six chimeras were able to complement the deletion mutations. These results suggest that each of the three domains of Rrp4p and Rrp40p are individually necessary to the structure and/or function of the multisubunit exosome complex, and that the domains of Rrp4p can not substitute for the very similar domain of Rrp40p and *vice versa*. These results are consistent with the proposed bridging interactions of Rrp4p and Rrp40p.

ABSTRACT

Animal Model of Endotoxin Induced Neurodegeneration in Parkinson's Disease

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Sponsored by: Roger Bick, PhD, Department of Pathology and Laboratory Medicine

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16

University of Texas Medical School at Houston - Office of the Dean

Key Words: Parkinson's disease, lipopolysaccharide, α -synuclein, tau, ubiquitin, cytokines

Parkinson's disease (PD) is a chronic relentlessly progressive neurodegenerative disease with no diagnostic test. PD is diagnosed via neurological examination after substantia nigra (SN) failure has ensued. In both animal and human models of sporadic PD, a neuroinflammatory process mediated by microglial activation from exposure to toxic substances, such as the bacterial endotoxin lipopolysaccharide (LPS), has been implicated in dopaminergic nigral cell loss and the degenerative process. An increased expression of proinflammatory cytokines by glial cells has been associated with PD. We hypothesized that exposure of adult rats to high concentrations of LPS would initiate an inflammatory process, in which specific neuronal areas demonstrate increased expression of cytokines and PD associated proteins (tau, α -synuclein, and ubiquitin). Adult rats were injected with 35 mg/kg LPS (IV); brains were removed after three hours, fixed, sectioned, and probed with specific antibodies for subsequent fluorescence deconvolution microscopy. Distributions of proteins and cytokines in specific areas were identified and fluorescence intensity measurements were made. The data revealed that high-dose LPS treatment results in a significant increase in tau, α -synuclein, and ubiquitin and increased expression of TNF α , IL-4, IL-10, IFN γ , IL-1 β , and IL-6 in the olfactory bulb and midbrain SN area. Our results suggest an inflammatory process in PD pathogenesis and indicate particular cytokines and protein distributions as not only markers of neurodegeneration, but as potential diagnostic adjuncts and therapeutic targets.

ABSTRACT

Investigating the Effects of Indomethacin (Indo) and Phosphatidylcholine (PC) in a Rodent Model of Necrotizing Enterocolitis (NEC)

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35 DK007676-16

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

Key Words: Necrotizing enterocolitis, indomethacin, phosphatidylcholine

NEC is the most common surgical emergency that affects the GI tract of premature infants. Neonates affected with this disease generally are being formula fed and have penetrating intestinal lesions, which frequently require surgery. Indo is an NSAID that is given to preterm infants to close the patent ductus arteriosus. As the use of indo has been associated with NEC, we hypothesize that indo will aggravate and PC, which is higher in breast milk than formula, will serve as a protecting agent against NEC. PC is structurally important for all cell membranes and fortifies the surface barrier of the GI tract. To test our hypothesis, NEC was induced in three day old rat pups by subjecting them to ten minutes of hypoxia two times daily. Additionally, for three days, they received varying dosages of indo or indo pre-associated with PC, which were injected subcutaneously. There was a significant difference in the bleeding between the control and indo groups, based upon hematocrit values of 0.296 and 0.260, respectively (standard errors of 0.013 and 0.009, $p=0.02$). PC attenuated the bleeding with a hematocrit value of 0.282. Additionally, the pups that had indo associated with PC had increased weight per unit length values for the ileum and colon compared to the treatment groups that only had indo, indicating less necrosis. These results support the hypothesis that PC protects against and indo exacerbates the development of NEC. Future studies are planned to validate and extend these observations.

ABSTRACT

Trials in Methodology: RNA Extraction from Formalin-fixed Lung Tissue in Tuberculosis Infected Mice and Humans

BRITTANY R. SERRATOS *The University of Texas at Houston Medical School Class of 2011*

Sponsored by: Robert L. Hunter, MD, PhD, Department of Pathology
Jeffrey K. Actor, PhD, Department of Pathology

Supported by: Robert L. Hunter, MD, PhD, Department of Pathology
University of Texas Medical School at Houston – Office of the Dean

Key Words: FFPE, tuberculosis, RNA extraction, xylene

Formalin fixed, paraffin embedded (FFPE) tissue samples were obtained from *Mycobacterium tuberculosis* infected lungs to investigate proinflammatory mediators during various stages of immunopathology. Methodological procedures were applied to isolate RNA from FFPE sections, in an attempt to match site-specific pathology with mRNA expression. Three protocols using mouse tissue were compared to examine efficiency and feasibility of mRNA recovery from tissue sections removed from prepared slides. Proinflammatory messages TNF- α , and stress regulating mRNAs β -HSDH1 and β -HSDH2, were examined by reverse transcriptase polymerase chain reaction (RT-PCR) and agarose gel analysis. Comparisons were made to housekeeping gene, β -actin. The first two protocols involved simply heating the tissue samples to dissolve the paraffin wax prior to mRNA extraction. One of these protocols examined the effect of PBS and EDTA on mRNA extraction efficiency, which were both added prior to heating. The most efficient procedure, involving the immersion of prepared slides in xylene, was used to examine different stages of human tuberculosis, extracting mRNA from FFPE sections. Proinflammatory and T-cell mRNAs TNF- α and IFN- γ were examined by RT-PCR and gel analysis, along with the housekeeping gene, hypoxanthine guanine phosphoribosyltransferase (HPRT). The RNA extraction procedure utilizing xylene for deparaffinization, subsequent washes with ethanol, and incubation with an RNA lysis buffer, was determined to be the most efficient method in comparison to standardized commercial kits. It is envisioned that these methods will allow accurate identification of proinflammatory markers and cytokines that correlate with stages of histopathology during tuberculosis infection.

ABSTRACT

Understanding of Cardiopulmonary Resuscitation by Surrogates of Critically Ill Patients

YURI SHIF

The University of Texas at Houston Medical School

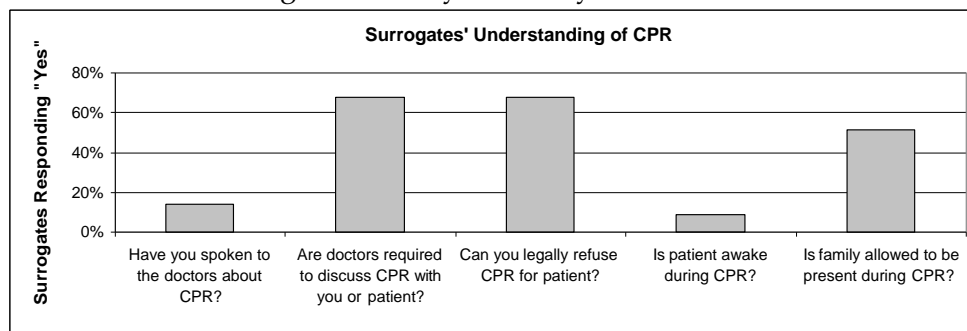
Class of 2011

Sponsored by: Khalid F. Almoosa, MD, MS
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Supported by: University of Texas Health Science Center – Office of the Executive Vice President for Academic Affairs
University of Texas Medical School at Houston – Office of the Dean

Key Words: CPR, surrogate, decision-making, ICU

PURPOSE: Decisions on end-of-life care in the ICU are often made by surrogates of critically ill patients. Since most ICU deaths occur after some limitation of life sustaining therapy, discussions on limiting cardiopulmonary resuscitation (CPR) are an important part of end-of-life decision-making. Consequently, surrogates' understanding of CPR may affect their decision to accept or decline CPR in the event of its need. Therefore, the objective of this study is to evaluate surrogates' understanding of the indications, process, and outcomes of CPR in ICU patients. **METHODOLOGY:** We administered an in-person questionnaire to ICU patients' surrogates at the Memorial Hermann Hospital MICU over a 2 month period. We identified critically ill patients based on their APACHE II score and ICU length of stay, and recruited their surrogates for the survey. **RESULTS:** Of 116 patients admitted to the ICU, 42 (36%) were enrolled. Cardiac arrest, respiratory arrest, or both were correctly identified as indications for CPR by 40%, 69%, and 34% of surrogates, respectively. Chest compression was a component of CPR correctly identified by 87% of surrogates, while electrical cardioversion and drug administration were each identified by 9%. The majority (71%) of surrogates believed patients had a greater than 75% survival rate after CPR. Broken ribs and bruising were identified as complications of CPR by 47% and 15%, respectively. **CONCLUSION:** A minority of surrogates have an accurate understanding of CPR, while most overestimated post-CPR survival. Such limited understanding of CPR may adversely affect end-of-life decision-making in the ICU.



ABSTRACT

AMP Kinase Activates Ubiquitin Ligases: A New Approach to Reverse Cardiac Hypertrophy

ROSS SHOCKLEY *The University of Texas at Houston Medical School Class of 2011*

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

Supported by: National Heart, Lung, and Blood Institute of the US Publish Health Service
(R01HL061483)

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

Key Words: LVH, Ubiquitin Proteasome System, AMPK

Left ventricular hypertrophy (LVH) is an independent risk factor for death and disability. Current strategies to reverse LVH focus on decreasing pro-hypertrophic signaling. This approach is unsuccessful because of the vast redundancy of the pro-hypertrophic signaling network. Here we propose a new way to reverse cardiac hypertrophy through the activation of pro-atrophic signaling pathways. The Ubiquitin Proteasome System (UPS) is the major signaling pathway responsible for skeletal muscle atrophy. The activation of the two muscle-specific ubiquitin ligases, Muscle Atrophy F-box protein (Atrogin-1/Mafbx) and Muscle Ring Finger 1 (MuRF-1), increase protein degradation *in vivo* and *in vitro*. Protein degradation is ATP-dependent. Because 5' AMP-Activated Protein Kinase (AMPK) is the cell's fuel gauge, we propose that AMPK plays a role in the regulation of Atrogin-1/Mafbx and MuRF-1, potentially reversing cardiac hypertrophy through the UPS. In order to investigate the role of AMPK in the activation of Mafbx and MuRF-1 *in vitro* and *in vivo*, we used two model systems: neonatal rat ventricular myocytes (NRVM) and C57BL/6 mice. When AMPK was activated with AICAR (5'-phosphoribosyl-5-aminoimidazole-4-carboxamide), Mafbx and MuRF-1 mRNA were induced in a dose- and time-dependent manner. The upregulation of these E3 ubiquitin ligases was reversed by an AMPK inhibitor, Compound C. The findings were reproduced *in vivo* using 9-week-old mice with one intraperitoneal injection of AICAR. Hearts of AICAR treated animals showed a significant increase in the expression of MuRF-1 mRNA and an increase in Atrogin-1/Mafbx mRNA. The data suggest that AMPK activates the UPS in cardiomyocytes.

ABSTRACT

MS-1 Medical Student

The Molecular Mechanisms Underlying The Protective Effects of BMP-7 Against Gastrointestinal Ischemia-Reperfusion Injury

STEPHEN P. STAMPP The University of Texas at Houston Medical School Class of 2011

Sponsored by: Tien C. Ko, MD, Department of Surgery
 Xianghua Liu, Ph. D, Department of Surgery
 Yanna Cao, MD, Department of Surgery

Supported by: Tien C. Ko: NIH P50GM038529 "Molecular pathogenesis of gut injury in multiple organ failure".
 University of Texas Medical School at Houston – Office of the Dean

Key Words: BMP-7, hydrogen peroxide, ischemia-reperfusion injury

Background: Ischemia-reperfusion (IR) injury refers to tissue damage that occurs as a result of the return of blood-flow after some critical period of arterial blockage. The absence of oxygen and nutrients leads to the accumulation of pro-inflammatory and cytotoxic metabolites. Following major trauma, IR injury to the intestine speeds a deadly progression toward multiple organ failure - the most common cause of late death in ICU patients. Bone morphogenetic protein (BMP)-7, a member of transforming growth factor (TGF)- β superfamily, has been known protective against ischemia in the brain, kidney and liver, though the underlying molecular mechanisms are largely unknown. Recently, our group has demonstrated that in rats, pretreatment with BMP-7 protected against intestinal damage and preserved function. To investigate the underlying mechanisms, rat intestinal epithelial cells (RIE-1) were chosen to test our hypothesis that BMP-7 protects against IR gut injury by promoting cell proliferation and inhibiting apoptosis.

Methods: RIE-1 cells were grown overnight in 5% dialyzed fetal bovine serum; serum starved for 4 hours; pre-treated with BMP-7 (1.6nM) for 5 hours. 500 μ M hydrogen peroxide (H₂O₂), which mimics IR injury, was added and the cells incubated for 24 hours. The WST-1 test was used to quantify cellular proliferation and a Cell Death Detection Elisa kit was used to measure DNA fragmentation, an indicator of apoptosis.

Results: The treatment of BMP-7, H₂O₂ alone, or combination of BMP-7 pretreatment and H₂O₂ altered cellular proliferation by 121.5%, 48.3% and 82.3% respectively, compared to control (100.0%). Correspondingly, DNA fragmentation of BMP-7, H₂O₂ alone or combination of BMP-7 pretreatment and H₂O₂ was induced with 0.90, 4.12, and 2.58 folds respectively compared to control (1 fold).

Conclusion: We have demonstrated that BMP-7 attenuated the deleterious effect of H₂O₂ on cellular proliferation and the induction of apoptosis by H₂O₂ in RIE-1 cells. These findings suggest that BMP-7 protects against gut injury by promoting proliferation and inactivating apoptotic process. Our study provides an *in vitro* model for further investigation into the molecular mechanisms underlying the protective effects of BMP-7 against IR injury in the gut.

ABSTRACT

CREB1 Expression in *Aplysia* Sensory Neurons Following Treatment with Serotonin

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Supported by: NIH grant NS01989S

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Key Words: CREB1, Long Term Facilitation, *Aplysia*, Serotonin

Long-term facilitation (LTF) of the synaptic connections between sensory neurons (SNs) and motor neurons is a key mechanism for the storage of memory. LTF requires the conversion of transient neuronal signals into long-term changes in gene transcription and protein expression. The transcription factor CREB1 has previously been identified as a potent regulator of LTF with the ability to positively regulate its own transcription, as well as the expression of CREB2 (a negative regulator of CREB1), and other proteins. CREB1 is known to be elevated in *Aplysia* pleural-pedal (sensory-motor) ganglia as long as 24 hours after treatment with serotonin, a transmitter that mimics the effects of behavioral training. However, until this study CREB1 expression in individual SNs at extended durations following serotonin treatment had not been evaluated. *Aplysia* sensory neuron cultures were treated with five pulses of serotonin (50 μ M) in 20-minute intervals and incubated for 24 hours. Cells were then fixed, treated with anti-CREB1 antibody, and stained with Alexa 568-conjugated secondary antibody. Images were acquired using confocal microscopy and CREB1 staining quantified using MetaVue[®] imaging software. At 24 hours, serotonin treated cells showed a 28.2% \pm 8.3 (p<0.05) increase in CREB1 staining as compared to controls. A sustained increase in CREB1 expression 24 hours after serotonin treatment in the SN suggests that CREB1 may continue to regulate gene expression and new protein synthesis long after the initial stimulus is delivered. Additional studies at times before and after 24 hours will further characterize the pattern of CREB1 expression in SNs and its role in long-term memory.

ABSTRACT

Determining the Learned Effect of the Functional Dexterity Test in Children

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Sponsored by: Gloria Gogola, MD, Shriners Hospitals for Children in Houston

Supported by: Thomas E Cain, MD Educational Trust Fund
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Key Words: Functional Dexterity Test, learned effect, Jebsen-Taylor Test, pediatric

BACKGROUND: Literature shows that commonly measured static parameters such as joint range of motion and pinch strength do not correlate with functional ability to complete tasks. Specific measures of dexterity and functional use are required to adequately assess an individual's hand. The Functional Dexterity Test (FDT) is a test of dexterity, validated in adults, that provides information on an individual's ability to use the hand for daily tasks.

PURPOSE: To determine the learning effect on validity and reliability of scores on the FDT in the pediatric population.

METHODS: Typically developing children aged 3 to 16 were recruited. Age, gender and hand dominance were recorded. They each performed 5 trials of the FDT board. The FDT board consists of 16 pegs arranged in a square. The score recorded is the time it took the subject to flip each peg over in their hand and replace it in the board. Penalties were recorded for using the board to turn the peg, touching the peg to the chest, dropping the peg, switching hands to turn the peg, helping turn the peg with the other hand, and supinating the hand while turning the peg.

RESULTS: 44 children were tested, with a mean age of 9.1 years (3.3 years to 16.9 years).

Time taken (seconds) per trial (mean \pm SD), with p-values for change inserted between trials:

	<u>Trial 1</u>	<u>p</u>	<u>Trial 2</u>	<u>p</u>	<u>Trial 3</u>	<u>p</u>	<u>Trial 4</u>	<u>p</u>	<u>Trial 5</u>
3 to 5 yo									
Raw time	40.4 \pm 13.9	.204	38.6 \pm 12.9	.519	39.5 \pm 13.0	.016	35.1 \pm 8.6	.705	34.4 \pm 6.6
Penalty time	32.5 \pm 30.0	.446	30.0 \pm 28.8	.546	23.9 \pm 26.8	.766	22.7 \pm 21.0	.381	26.4 \pm 23.3
Total time	72.9 \pm 37.7	.153	68.6 \pm 35.1	.568	63.5 \pm 35.1	.274	57.8 \pm 24.4	.560	60.9 \pm 25.2
6 to 8 yo									
Raw time	28.2 \pm 3.6	<.000	24.8 \pm 3.8	.029	23.8 \pm 3.8	.456	23.5 \pm 4.0	.643	24.1 \pm 4.3
Penalty time	24.4 \pm 26.2	.369	15.6 \pm 11.8	.677	13.3 \pm 11.2	.880	12.8 \pm 12.3	.386	19.4 \pm 15.9
Total time	52.6 \pm 28.9	.221	40.4 \pm 11.2	.560	37.1 \pm 12.0	.827	36.3 \pm 13.2	.406	43.5 \pm 17.4
9 to 12 yo									
Raw time	24.4 \pm 6.6	.001	21.9 \pm 5.7	.284	21.2 \pm 4.8	.425	20.7 \pm 4.0	.219	19.9 \pm 4.0
Penalty time	5.0 \pm 3.9	.082	2.3 \pm 3.4	.046	5.5 \pm 6.1	.810	5.0 \pm 7.1	.999	5.0 \pm 5.0
Total time	29.4 \pm 7.5	.005	24.2 \pm 7.9	.194	26.7 \pm 10.0	.682	25.7 \pm 8.2	.715	24.9 \pm 7.3
13 to 16 yo									
Raw time	22.6 \pm 3.6	.091	21.1 \pm 3.4	.040	19.6 \pm 2.6	.287	19.2 \pm 2.4	.149	17.8 \pm 2.8
Penalty time	4.5 \pm 8.6	.370	1.5 \pm 3.4	.373	3.5 \pm 6.3	.138	1.0 \pm 2.1	.394	2.5 \pm 6.3
Total time	27.1 \pm 11.3	.257	22.6 \pm 5.2	.827	23.1 \pm 7.1	.125	20.2 \pm 3.2.851	19.7	\pm 8.2

CONCLUSIONS: Data has shown that the times stop changing significantly after the 2nd trial for all pediatric age groups except our youngest sampling, ages 3 to 5. The times in this age group stopped changing significantly after a 3rd trial.

SIGNIFICANCE: This study represents the first step in the validation of the FDT in the pediatric population. The next steps are validation of the FDT in children with congenital hand anomalies, and establishing normative scores for the FDT in typically developing children. Based on this study the FDT shows promise as a rapid and reliable clinical instrument for children with congenital hand deformities for planning treatment, surgical decisions, and follow-up care.

ABSTRACT

Gastric Bypass, but not Gastric Banding, Induces Sustained Weight Loss and Reversal of Insulin Resistance in Severely Obese Patients

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Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 2 T35
DK007676-16

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Key Words: Bariatric surgery, obesity, insulin resistance, adipokines

Background: Bariatric surgery reverses obesity-related comorbidities, including type 2 diabetes mellitus. Several studies have already described differences in anthropometrics and body composition between Roux-en-Y (RYGBP) and laparoscopic adjustable gastric banding patients (LAGB), but the role of adipokines in outcomes after the different types of surgery is not known.

Hypothesis: Differences in weight loss and reversal of insulin resistance exist between the two groups and correlate with changes in adipokines. **Methods:** Fifteen severely obese women (mean BMI: 46.7 kg/m²) underwent weight loss surgery (RYGBP = 10, LAGB = 5). Weight, waist and hip circumference, body composition, plasma metabolic markers, and lipids were measured at set intervals during a 24-month (24M) period after surgery. **Results:** At 24M, RYGBP patients were overweight (BMI 29.7 kg/m²) while LAGB patients remained obese (BMI 36.3 kg/m²). RYGBP patients lost significantly more fat mass than LAGB patients (mean difference 16.8 kg, $p < 0.05$). Significant differences were seen in leptin levels between the surgery groups at 24M ($p = 0.003$). Leptin correlated with weight loss, fat mass loss, insulin levels, and HOMA-IR. Adiponectin correlated with insulin and HOMA levels ($r = -0.653$, $p = 0.04$ and $r = -0.674$, $p = 0.032$, respectively) at 24M in the RYGBP patients.

Conclusions: Gastric bypass, but not gastric banding, induces sustained weight loss and reversal of insulin resistance in severely obese patients. Both parameters are accompanied by a normalization of adipokine levels.

ABSTRACT

Visualization of Cortical Lesions in Multiple Sclerosis

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Supported by: The Foundation of the Consortium of Multiple Sclerosis Centers / Band
Against MS Foundation Summer Research Scholarship
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Key Words: Multiple Sclerosis, Cortical Lesion, MRI, Double Inversion Recovery, 1.5 Tesla

Traditionally, MS was viewed as a consequence of white matter demyelination. Cortical lesions were not routinely observed ante-mortem until the advent of 3T MRI. 3T imaging, although superior in quality to 1.5T in terms of greater signal-to-noise ratio and improved spatial resolution, is not widely available. Detection of cortical lesions is important in understanding their role in disease progression and clinical manifestations of MS.

A retrospective study was conducted to determine if 1.5T 2D double inversion recovery (DIR) images are sensitive to cortical lesions. DIR has two inversion pulses, which attenuate CSF and white or gray matter depending on the sequence. 33 brain scans collected between 1997 and 2000 using a GE 1.5T scanner were evaluated. Hyperintense signals on white matter suppressed DIR images were compared with images from co-registered T2, gray matter suppressed DIR, and FLAIR sequences. Lesions were classified as purely intracortical, mixed meaning predominantly gray matter involvement, or juxtacortical meaning lesions with extension into gray matter.

33 scans yielded 19 intracortical, 35 mixed, and 32 juxtacortical lesions. Gray matter suppressed DIR is useful for classifying hyperintensities seen on white matter suppressed DIR as mixed or juxtacortical. Purely intracortical lesions are difficult to visualize because of low signal to noise ratio and indistinct boundaries between gray and white matter. Additionally, low resolution and high artifact make it difficult to identify and confirm the presence of intracortical lesions. In conclusion, 1.5T 2D DIR is not reliable for detecting intracortical lesions. The 19 suspected intracortical lesions found could possibly be artifact. No correlation between quantity of lesions and EDSS scores was observed.

ABSTRACT

Glomerular Expression of CD300 Proteins in the Mouse Kidney

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Supported by: Michael Braun, MD, Department of Pediatrics
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Key Words: “Immune complex”, “lupus”, “kidney”, “mice”

Immune complex (IC) deposition is found in nearly half of the patients who present with a renal glomerulopathy, including IgA nephropathy, membranous nephropathy, and lupus nephritis. While IC deposition is clearly evident in patients with these diseases, the mode of deposition is not fully understood. In order to understand these mechanisms, we have investigated whether proteins in the CD300 family may act as renal receptors for ICs. These proteins display sequence homology to classical Fc-receptors and Ig-transporters. Moreover, one of these proteins, CD300g, has been identified as an Ig transporter in the heart.

RT-PCR showed expression of CD300g and CD300c in glomeruli, but only CD300g mRNA was seen in mesangial cells. Immunostaining was performed on paraffin and frozen heart and kidney sections using indirect immunofluorescence. Glomerular expression was confirmed for CD300g, and examination by confocal microscopy localized the staining to glomerular endothelial cells. Immunostaining for CD300c was unable to validate the mRNA data. Western blots were also done using mesangial cell, podocyte, glomerular endothelial cell, and whole kidney lysates. Several proteins expressed by mesangial cells, with an affinity for the anti-CD300c antibody, were detected, supporting CD300c expression in the glomerulus.

Although more investigation needs to be done, it appears that CD300c and CD300g are expressed in different cell populations within the kidney, suggesting that each protein may mediate cell-specific responses to circulating ICs. These findings may lead to a better understanding of IC diseases and thus may give us an opportunity to uncover new approaches for managing these diseases in humans.

ABSTRACT

Measuring antibodies to the EA antigen of Epstein-Barr virus in Multiple Sclerosis

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Supported by: John W. Lindsey, MD

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Key Words: Multiple Sclerosis, Epstein-Barr Virus, Early Antigen

Multiple sclerosis (MS) is an autoimmune disease that destroys myelin in the central nervous system. The etiology of MS is unknown, but infection with Epstein-Barr virus (EBV) is a possible cause. Antibodies against the nuclear antigen of Epstein Barr virus (EBNA) remain elevated lifelong after primary infection and many studies have shown that EBNA antibodies are increased in MS. Antibodies against EBV early antigen (EA) decrease with resolution of the primary infection, and increased titers are supposed to correlate with reactivation of infection. Some, but not all, investigators have reported an increase of EA antibodies in MS. Increased EA antibody would indicate more active EBV infection in MS and intensify the relationship of EBV and its possible disease-causing role in MS patients. The purpose of this research was to determine whether EA antibodies are increased in the serum samples of MS patients vs controls.

We compared 84 MS patients with controls matched for gender, ethnicity, and ± 5 years of age. We also compared samples taken from 19 MS patients during a clinical relapse and while stable. Testing of antibody titers was performed following the instructions of the EBNA and EA IgG ELISA kits from the Wampole company. We also modified the ELISA kit to test for IgA. The results were obtained by reading the optical density of the samples using an ELISA reader.

EBNA antibody titers in MS patients were higher than controls ($p=0.0227$, paired-t test), which was similar to previous research findings. However, we did not find differences in the EA antibody titers ($p=0.6683$). In addition, the EA antibody titer did not increase during clinical relapse in MS patients ($p=0.3168$). We concluded that EA antibodies do not correlate with MS relapses. The experiment for IgA is continuing and will be presented.

ABSTRACT

Mortality in Patients with Unilateral and Bilateral Femur Fractures

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Supported by: UT-Houston Medical School Department of Orthopaedics
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Key Words: Bilateral, femur, mortality

Objectives: To determine the effect of and investigate the differences between unilateral and bilateral femur fractures on patient mortality.

Study Design: Retrospective analysis using trauma registry data and electronic medical records of blunt trauma patients with unilateral (1519 patients, Group I) or bilateral (75 patients, Group II) femur fractures.

Methods: Univariate analysis was used to investigate femur fractures as a direct cause of mortality. Multivariate logistic regression was used to determine the effect of femur fractures on mortality and determine other variables statistically associated with mortality.

Results: Observational analysis showed that femur fracture was not the recorded cause of death for any of the mortalities. In addition, chi-square analysis ($p=.843$) and logistic regression ($p=.677$) show that femur fractures in no way correlate significantly with a specific cause of death. Group II patients have a higher incidence of mortality than Group I patients (21.4% versus 6.8%). Univariate logistic analysis showed a significant difference in mortality between Group I and Group II patients (odds ratio = 3.47, $p<0.001$). However, a model was calculated using multivariate logistic analysis which included ISS ($p<0.001$), age ($p<0.001$), sex ($p=0.037$), and days in the ICU ($p=0.004$). Once adjusted for these significant correlating variables, the contributing difference to mortality between unilateral and bilateral fractures lost its significance (odds ratio = 2.14, $p=.066$).

Conclusions: Neither unilateral nor bilateral femur fractures are direct causes of death. Rather, femur fractures can be used as an indicator of the risk of mortality, because patients with femur fractures have sustained significant trauma that can lead to death. Also, the incidence of mortality for patients with both unilateral and bilateral femur fractures has decreased from data previously published. And, although there is an increased risk of mortality for Group II patients versus Group I, an equally accurate model can be obtained ignoring femur fractures and considering ISS, age, sex, and days in the ICU.

ABSTRACT

Inflammatory response to intraventricular hemorrhage: The effect of tissue plasminogen activator

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Supported by: UTHSC-Houston Dept. of Neurology
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Key Words: Intraventricular hemorrhage, tissue plasminogen activator, inflammation

Background: Intracranial hemorrhage (ICH) accounts for a third of all strokes. In 45% of cases the hematoma extends as intraventricular hemorrhage (IVH) - a known predictor of poor outcome. Intraventricular inflammation is believed to be one mechanism by which IVH exerts its deleterious effects. Tissue plasminogen activator (tPA) delivered directly into the ventricles via ventriculostomy has been studied for treatment of IVH. While tPA may accelerate the clearance of IVH, its effect on IVH-induced inflammation is unknown. The purpose of this work was to describe the inflammatory response in the CSF following IVH and compare it in patients treated with intraventricular tPA.

Methods: Patients diagnosed with IVH and treated with ventriculostomy were selected from the stroke registry. Data on several markers for both CSF and systemic inflammation for 19 days post-IVH were captured. We examined marker trends for tPA and non-tPA treated patients.

Results: 51 patients were identified: 29 in the tPA and 22 in the non-tPA group. Blood markers showed no evidence of systemic inflammation. CSF data are shown in the table:

CSF Variable (normal)	Non-tPA peak value	tPA peak value	P-value
Glucose (45-90)	85.9	81	.39
Protein (15-45)	237.7	209	.32
Lactate (0.6-2.2)	4.6	4.2	.25
WBC (0-5)	444	645.4	.58
RBC (0)	219433	281444	.54

One patient in the tPA group had a positive CSF culture. The combined data showed signs of inflammation in several CSF markers (protein, lactate and WBC count), which peaked around day 3-5, and fell off by the end of the 19-day study. tPA treatment had no effect on the inflammatory markers.

Conclusions: IVH induces intrathecal inflammatory response that peaks at day 3-5 from the hemorrhage. Intraventricular tPA does not seem to modify or aggravate this inflammatory response.

ABSTRACT

Prevalence of Diabetes Mellitus in Division 1 College Athletes

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Supported by: Department of Orthopaedics
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Key Words: Diabetes, college, athletics, NCAA, orthopaedics

Background: Diabetes mellitus is associated with a number of serious complications. Although extensive research has been done on these problems in patients with diabetes mellitus, there has been very little focus on these issues specifically among young, physically active adults. The main objective of this proposed project is to determine the number of NCAA programs that have athletes with diabetes.

Materials and Methods: To determine the number of athletes with diabetes, 1012 NCAA athletic programs' sports medicine departments were contacted by email and phone to determine which programs had athletes with diabetes mellitus during the 2007-2008 season.

Results: 42% of schools responded to the survey. 41% of the schools that responded reported that they did have athletes with diabetes mellitus during the 2007-2008 season. The survey identified a minimum of 221 athletes participating in NCAA sports with diabetes mellitus. When categorized by NCAA division, 72% of Division 1 schools responded with 42% of responding schools reporting athletes with diabetes. 38% of Division 2 schools responded with 33% of responding schools reporting athletes with diabetes. 20% of Division 3 schools responded with 46% of responding schools reporting athletes with diabetes.

Conclusions: A large percentage of NCAA athletic programs have athletes with diabetes, making knowledge of the proper management and care of athletes with diabetes essential for athletic trainers and sports medicine staff in college athletic programs.

ABSTRACT

Differential Effects of Obesogenic Diets on Rat Heart: Western Diet Increases the Ratio of Saturated to Unsaturated Fatty Acyl-CoAs and Impairs Contractile Function

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Supported by: NHLBI RO1-HL073162 and the Dean's Office

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Key Words: Obesity, metabolism, heart, lipotoxicity

Background: Obesity is a state of impaired energy homeostasis and a risk factor for heart disease. Recent evidence suggests that diet composition may be a critical determinant of long-term adaptation or maladaptation of the heart in obesity. We found that cardiac power was decreased in rats fed “Western” diet (WD), but not in rats fed either low-fat (LFD) or high-fat diet (HFD).

Hypothesis: WD results in a specific pattern of metabolic derangements which will trigger cardiac dysfunction.

Methods: Wistar rats were fed LFD, WD, or HFD (10, 45, and 60% calories from fat respectively) for acute (1 day to 1 week), short (4–8 weeks), intermediate (16–24 weeks), or long (32–48 weeks) term. Insulin, leptin, and triglyceride plasma levels were measured by radiometric and spectrophotometric assays. Cardiac glycogen and lipid byproducts were quantified by enzymatic assays and HPLC.

Results: With time, there was a gradual increase in insulin and triglyceride plasma levels in animals fed HFD, WD, and LFD respectively. Leptin levels increased in parallel with increases in mesenteric fat mass. Of the six LCFA-CoA species analyzed, five were significantly increased with WD. This change was accompanied by a significant decrease in the ratio of unsaturated to saturated LCFA-CoAs.

Conclusions: Although plasma parameters are not significantly different between WD and HFD, the former induces a dramatic change in the intramyocardial LCFA-CoA composition. The heart's metabolic response to obesogenic diets is complex. Future studies will determine exact mechanisms underlying cardiac failure in WD.

INTERNATIONAL MEDICAL STUDENTS

ABSTRACT

The Specificity of Uba6-activated Ubiquitin Signaling Pathway

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Class of 2013

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

Key Words: ubiquitin signaling pathway, Uba6, Use1

Ubiquitylation is one of the most important post-translational modifications of proteins. It controls many essential signaling networks by regulating the stability, function, and intracellular localization of many proteins in eukaryotes. This process is mediated by three enzymes, E1, E2 and E3, which make up the E1-E2-E3 cascade. Uba6 is a new E1 enzyme that was discovered recently in higher organisms. Uba6 initiates its specific ubiquitin signaling pathway through a unique E2 enzyme, Use1. In contrast, Uba1, the first identified E1 for ubiquitin, can activate its own E2, Cdc34, but not Use1. Use1 and Cdc34 share a common E2 domain called UBC, but Use1 has a long N-terminal domain that is unique in the family of E2 enzymes. In order to evaluate the role of the N-terminal domain in directing the specificity of Use1, we mutated Use1 by PCR-based in vitro mutagenesis, then expressed and purified the wild type and mutant proteins in bacteria. The purified Use1 proteins will be applied in protein assays, such as in vitro transthiolation, to compare the activities of wild type and the mutant enzymes in E1-E2 specificity control.

ABSTRACT

Bcl-2 overexpression prevents odontoblast differentiation

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Sponsored by: Wenjian Zhang, PhD, Assistant professor, Department of Diagnostic Sciences

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

Key Words: Bcl-2, odontoblast, differentiation, real-time PCR

Bcl-2, an anti-apoptotic gene, is important in odontogenesis. This study was aimed to examine how Bcl-2 overexpression affected odontoblast differentiation in primary dental pulp cultures. Pulp cell cultures derived from 5-day-old wild-type (+/+) and transgenic (tg/tg) Col2.3Bcl-2 mice were established. Under confluence (day 7), the cells were boosted with 10⁻⁸M dexamethasone, 8mM β-glycerophosphate and 50μg/ml ascorbic acid for 1 day, then the medium was supplemented with 4mM β-glycerophosphate and 50μg/ml ascorbic acid and changed every other day to induce odontoblasts differentiation. On days 7, 14 and 21, total RNA was extracted and transcript expressions of type I collagen (Col1a1), osteocalcin (OC), dentin sialophosphoprotein (DSPP), dentin matrix protein-1 (DMP-1), and core bonding factor alpha-1 (Cbfa-1) were detected by real-time PCR. Glyceraldehyde 3-phosphate dehydrogenase was internal control. For odontoblast specific markers DMP-1 and DSPP, both +/+ and tg/tg showed increased expressions with time, and tg/tg expressed 7%, 46%, and 3% of DMP-1, and 7%, 86%, and 17% of DSPP as in +/+ on days 7, 14, and 21, respectively. For common markers Col1a1 and OC, +/+ showed a decreasing while tg/tg maintained an increasing trend, and tg/tg expressed 7 and 113 times higher of Col1a1, and 27 and 31 times higher of OC than +/+ on days 14 and 21, respectively. For the transcriptional factor regulating odontoblast differentiation, Cbfa-1, tg/tg expressed 32% that of +/+ on day 7, but more similar to +/+ later on. In conclusion, odontoblast-targeted Bcl-2 overexpression impaired their differentiation, probably via an initial inhibition of Cbfa-1.

ABSTRACT

The effects of G-CSF on microglia/macrophages after intracerebral hemorrhage

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

Key Words: G-CSF hemorrhage microglia

Inflammation after intracerebral hemorrhage (ICH) is considered an important component of damage caused by ICH. Granulocyte colony-stimulating factor (G-CSF) is a cytokine used in the treatment of hematologic disorders such as neutropenia; however, its role in inflammatory-mediated brain damage is less clear. Therefore, in this project, we studied the effect of G-CSF on brain inflammation caused by ICH (using the intra-cerebral blood injection model).

G-CSF (50 µg/kg, i.p.) or saline was injected at 2 h after ICH and then every 24 h for 3 days. Three days after ICH, the mice were sacrificed for histological analysis and measurement of mRNA and protein levels to assess inflammation.

Using immunohistochemical analysis, we found that G-CSF was effective in reducing the number of microglia/macrophages in the ICH-injured brain (CD68 positive cells). This result was further confirmed using RT-PCR analysis that demonstrated significant reduction in CD36 and CD68 mRNA expression in the peri-ICH brain tissue of G-CSF treated mice. In addition, we found that G-CSF reduced the level of mRNA of pro-inflammatory cytokines, IL-1 β and TNF α in ICH-injured brain.

Furthermore, we isolated microglia from mice (1~2 days after birth), and tested whether G-CSF (50ng/ml) can affect phagocytotic properties of microglia, using red blood cell phagocytosis as a target of phagocytosis. This study demonstrated that G-CSF did not change the phagocytotic properties of microglia

In summary, our data suggest that G-CSF is effective in reducing inflammation after ICH and therefore may be considered as potential treatment for ICH.

ABSTRACT

A Unique Angiogenesis Present in the Aortic Walls of the Ascending Aorta in TAA Patients without Dissections

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

Key Words: TAA, Angiogenesis, Vasa vasorum, Media

Background- Thoracic aortic aneurysms (TAA) are characterized by fragmentation of elastic fibers and increased proteoglycans. These and other factors cause the vessel wall to weaken and eventually tear. Recently, a unique patient was found with rapid progression of TAA. Increased vasa vasorum (feeding vessels for blood vessels) was found, especially in the media (middle layer) of the aorta. Normally, the vasa vasorum are found in the adventitia (outer layer) and along the adventitial/medial border.

Hypothesis- We hypothesize that increased angiogenesis is present in the media of TAA patients, and this may weaken the vessel wall and increase the risk of dissection.

Methods- We immunostained aortic tissue from 8 controls and 10 TAA patients using von Willebrand Factor antibody, an endothelial cell marker. We calculated the numbers and areas of positively stained vessels in the media, and along the adventitial/medial border. All calculations were done using equal areas of tissue in patients and controls.

Results- There were significantly more vessels in the media and along the adventitial/medial border in patient aortas than in controls ($p < 0.05$). Interestingly, no medial vessels were observed in control aortas. The total area of the vessels was also greater in patients compared to controls ($p < 0.05$).

Conclusions- Increased vascularity was present in the aortic wall of patients with TAA. This increased vascularity, along with other factors, may weaken the vessel wall and increase the risk of dissection.

Future work- Future studies will clarify the key molecules and mutations leading to the observed increase in angiogenesis.

ABSTRACT

Investigation of RNAi therapy for Pseudoachondroplasia

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

Key Words: Pseudoachondroplasia, PSACH, COMP

Pseudoachondroplasia (PSACH) is a birth defect characterized by short stature, abnormal joints and early-onset osteoarthritis. PSACH is caused by mutations in cartilage oligomeric matrix protein (COMP), which is an extracellular matrix protein expressed primarily in cartilage, ligament and tendon. COMP mutations are associated with unsuccessful protein folding and export, and protein retention leads to premature chondrocyte death. However, COMP null mice are phenotypically normal indicating that COMP is not necessary for skeletal development. Therefore, we hypothesize that reducing expression of mutant and wild type COMP in affected chondrocyte using short hairpin RNAs (shRNAs) techniques can prevent intracellular accumulation of COMP and resolve the PSACH cellular phenotype. To test the hypothesis, COS7 cells are first infected with COMP-targeted shRNA in lentiviral particles. Puromycin is used to select for integration. COS7-shRNA cell lines are subsequently infected with adenovirus that expressed either wild-type (WT) or mutant-type (MT) COMP in response to doxycycline (DOX). This adenoviral system recapitulates the *in vivo* cellular phenotype of PSACH very closely. Protein and RNA levels are assessed respectively by Western blot and Northern blot analysis. These experiments both show significant reduction in COMP protein and RNA levels even when high dose of DOX is administered. As a result, shRNA therapy may be developed for humans and reduce COMP expression efficiently during skeletal growth when COMP expression is highest.

ABSTRACT

Analyzing a role for 53BP1 in common fragile site expression

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Sponsored by: Phillip. B. Carpenter, PhD, Department of Biochemistry and Molecular Biology

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

Key Words: 53BP1, common fragile site, pRS shRNA expression vectors

p53 binding protein1 (53BP1), a mediator of the DNA damage checkpoint influences cell cycle checkpoints and localizes to stalled DNA replication forks in S phase. Because common fragile sites are often expressed in response to replication stress, we hypothesize that 53BP1 may maintain common fragile site stability. To examine the nature and expression of common fragile sites, we constructed cell lines that specifically abrogate 53BP1 expression through the use of RNA interference.

The pRS shRNA expression vectors have a number of features allowing stable transfection, as well as the stable delivery of the shRNA expression cassette into host cells via a replication-deficient retrovirus. A puromycin-N-acetyl transferase gene is located downstream of the SV40 early promoter, resulting in resistance to the selection of the antibiotic puromycin. The shRNA expression cassette consists of 29 bp 53BP1 specific sequences, a 7 bp loop, and another 29 bp reverse complementary sequence, all under human U6 promoter. The transformation of the plasmids into competent cells DH5 α and extraction of plasmids followed the routine processes. Transfected pRS shRNA expression vector into HCT116p53^{+/+} as well as HCT116p53^{-/-} cells, selected for stable clones by medium containing 10% FBS plus puromycin at 48h post-transfection.

ABSTRACT

Is iNOS also a superoxide synthase?

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Class of 2005

Sponsored by: Ah-Lim Tsai, Ph.D., Internal Medicine, Hematology

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

Key Words: inducible NOS, superoxide, peroxynitrite

Nitric oxide (NO) plays an important role in vasodilation, neurotransmission and immune surveillance. Among the three NOS isozymes, the inducible NOS (iNOS) is responsible for high level (μM) NO biosynthesis for the purpose of cytoprotection. In addition to NO, formation of other reactive radical intermediate such as superoxide catalyzed by iNOS is an interesting but controversial subject. Some studies indicate that iNOS lacks the ability to produce superoxide but their results might be the consequence of excess 5, 6, 7, 8-tetrahydrobiopterin (BH_4) cofactor, which can directly react with superoxide. As the other two NOS isoforms showed abundant superoxide formation, we propose that iNOS can be a superoxide synthase depending on the supply of BH_4 and substrate L-arginine. To test our hypothesis, bacterial expression of iNOS and iNOS oxygenase domain (iNOS_{ox}) were used in our experiment. Either CAM or GroEL chaperone is coexpressed to obtain iNOS protein samples in proper folding. Ni^{+2} affinity column is used to purify the recombinant proteins. Rapid freezing quench EPR kinetic measurements for the reaction between ferrous iNOS and oxygen in the presence and absence of BH_4 or L-arginine will characterize the formation of radical intermediates in addition to BH_4^{\bullet} and NO. We expect that iNOS can form superoxide in the absence of BH_4 or/and L-arginine. Formation of superoxide of iNOS has special significance as superoxide reacts with NO to form very potent peroxynitrite that leads to chemical modification of many biological macro molecules, a process leading to inflammation and other diseases.

ABSTRACT

Amphetamine Sensitization is Prevented by Prefrontal Cortex Lesion

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Class of 2008

Sponsored by: Nachum Dafny, PhD, Department of Neurology and Anatomy

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

Key Words: Behavioral sensitization; Amphetamine; Prefrontal cortex; Lesion

The psychostimulant amphetamine (Amph) and methylphenidate (MPD) have been the treatment of choice for Attention-deficit hyperactivity disorder. Chronic moderate exposure to psychostimulants induces behavioral sensitization. Recent MPD studies suggest that the prefrontal cortex (PFC) is involved in behavioral sensitization.

The objective of this study was to investigate the acute and chronic effect of Amph before and after electrolytic PFC lesion using the open field assay. Male Sprague-Dawley rats were divided randomly into three groups, (1) an intact control group, (2) a sham group, and (3) a lesion group. On experiment day 1, all animals were injected with saline and recorded. On experiment day 2, lesion group received bilateral electrolytic lesions of PFC while sham group received the same surgery without current. After 5 days of recovery, all animals were injected with saline and recording were resumed. On experiment day 9 to 14, all animals were daily injected with single dose of 0.6 mg/kg amphetamine. Experiment day 15 to 17 were washout period, no injection was given but recording were resumed at the same time of the previous days. The re-challenge injection of 0.6 mg/kg amphetamine was given on day 18.

All the three groups showed increases in locomotor activity in acute amphetamine injection. Following chronic amphetamine, the control group and sham group exhibited behavioral sensitization while the PFC lesion group failed to express behavioral sensitization. These results suggest that PFC lesion does not interfere with the acute effects of amphetamine on locomotor activity but is required for development of behavior sensitization.

ABSTRACT

The effect of Lactoferrin treatment on *E.coli* proliferation and blood pressure in mice

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Class of 2010

Sponsored by: Jeffrey K. Actor, PhD, Department of Pathology and Laboratory Medicine

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

Key Words: Lactoferrin, LPS, systemic inflammatory response syndrome, inflammation

Lactoferrin is a natural iron binding glycoprotein found in high concentrations in most exocrine secretions and within secondary granules of neutrophils. It is known that Lactoferrin demonstrates protective effects to lipopolysaccharide (LPS) induced endotoxic shock, through mediation of host immunoregulatory responses. The overall goal of this project is to develop a clinical protocol for treatment of systemic inflammatory response syndrome (SIRS) using human or bovine Lactoferrin. Experiments were performed to investigate the immediate effect of Lactoferrin on proliferation of *E.coli* using LPS (+) SM105 and LPS (-) SM101 strains. Bovine Lactoferrin demonstrated a dose response reduction in proliferation of *E.coli*. Human Lactoferrin also resulted in similar decreases in proliferation, however, the inhibition was to a lesser extent than observed for bovine Lactoferrin. No Lactoferrin mediated inhibition in bacterial proliferation was demonstrated when using the SM101, LPS deficient strain. These results suggest that the sensitivity to Lactoferrin on *E. coli* proliferation was related to LPS. Because of the known immunoregulatory effect of Lactoferrin on oxidative stress, the ability of both bovine and human Lactoferrin to moderate blood pressure and heart rate were also examined in vivo. Human Lactoferrin administered intraperitoneally was shown to reduce blood pressure, with an especially persistent fall in diastolic blood pressure. Treatment with bovine Lactoferrin did not demonstrate similar changes. Overall, these experimental help to define a role for Lactoferrin as a therapeutic agent in control of events during endotoxic shock due to Gram negative infectious agents.

ABSTRACT

Genetic Association Studies in Ankylosing Spondylitis Identify Non-MHC Genetic Determinants of Disease Susceptibility

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Sponsored by: Xiaodong Zhou, M.D.; Department of Internal Medicine and Rheumatology

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

Key Words: Ankylosing Spondylitis(AS), genetics, SNPs, ARTS1, IL23R

Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disorder primarily affecting the axial skeleton. Although, HLA-B27 strongly contributes to the susceptibility of AS, multigenic inherited components are evident in this disease. Recently, while examining 1000 AS cases of white European descent from British using Illumina HumHap300 microarray genotyping slides, we identified that 130 SNPs across entire human genome are associated with AS. This study aimed to verify the association of these SNPs with AS patients from a North American cohort.

Methods: 810 AS cases vs. 580 controls from US and 650 AS cases vs. 600 controls from Canada were enrolled. Cases and controls were genotyped with ABI SNPlex assays and TaqMan assays. Raw data were analyzed with GeneMapper V4 for SNPlex and SDS 2.2 program for TaqMan assay. Case-control analysis was then performed by Chi square and Fisher's exact tests.

Results: Association was confirmed in the North American cohort for the SNPs from both the ARTS1 and IL23R genes with $P < 0.05$ for all markers genotyped. At ARTS1, peak association was seen with SNP rs30187 (odds ratio (OR) = 1.34, $p = 5.7 \times 10^{-5}$). At IL23R, the peak association was seen with SNP rs134151 (OR=0.74, $p = 6.1 \times 10^{-5}$). Analysis of the SNPs corresponding to other genes, such as IL1R2 and TNFRSF, is still in progress.

Conclusions: Studies reported here confirmed that in addition to HLA-B27, several other genes also contribute to AS susceptibility. ARTS1 is an aminopeptidase involved in trimming peptides to the optimal length for MHC Class I presentation. It is an important regulator of inflammatory process in trimming cytokine receptors including receptors for IL-1, IL-6 and TNF. IL23R is also an inflammatory associated gene that has regulatory role in the function of Th17 lymphocytes. These newly identified AS genes provide not only important information for potential disease pathogenesis, but also possibility of targeted cytokine blockade as a novel treatment for the condition.

UNDERGRADUATE STUDENTS

ABSTRACT

A Study to Assess Meibomian Gland Function and Ocular Tear Film Stability after Electrostimulation in Patients with Meibomian Gland Dysfunction

KHALID T. AL-KALLA The University of Texas at Houston Medical School Class of 2012

Sponsored by: Richard Yee, MD, Department of Ophthalmology

Supported by: Richard Yee, MD, Department of Ophthalmology
University of Texas Medical School at Houston – Office of the Dean

Key Words: Meibomian Gland, Tear Film, Orbicularis muscles,

Background: Meibomian gland dysfunction is often linked with lid margin vascularization, obstructed orifices, and decreased secretion of the meibomian glands (MGs) in the eyelids. If the orifices on the rim of the eyelids remains hindered, meibum (lipid) secretion is reduced across the ocular surface leading to tear film instability. Therefore, inducing orbicularis muscles, located on the periocular surface of the eyelids, may improve MG secretion.

Purpose: The aim of the study is to assess the effectiveness of low voltage electrostimulation of the muscles in the lower eyelids to increase secretion by the MG.

Method: Five subjects were recruited into this pilot study. The subjects completed a pre- and post-treatment evaluation. They completed an ocular surface disease index (OSDI) questionnaire, underwent tear evaporation rate assessment, and standard clinical tests for MG function. Tear film lipid layer interferometry videos and confocal microscopy images were also taken to assess tear film stability. Electrostimulation was then applied to the orbicularis muscles in the lower eyelid of the treatment eye for a total of 15 minutes, three times a week over a two week period.

Results: Post-treatment results displayed a significant decrease in the obstruction of the lower lid of the treated eye ($p=0.034$). TBUT, Confoscan score, basal tear test, OSDI values and vascularity in upper & lower lids also improved although not statistically significant ($p=0.184$, 0.374 , 0.843 , 0.344 , 0.208 , & 0.587 respectively).

Conclusion: The results indicated that short-term low voltage electrostimulation of the orbicularis muscles lessened obstruction and improved secretion levels of the MG.

ABSTRACT

Determining IRF7 expression in Scleroderma Fibroblasts in the Presence of Interferon

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Sponsored by: Sandeep K. Agarwal, MD, PhD, Department of Rheumatology

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

Key Words: IRF7, scleroderma, IFN

An increased type I interferon (IFN) signature has been observed in the peripheral blood cells of scleroderma patients. The experiment was designed to determine if IFN alpha differentially regulates gene expression of dermal fibroblasts from scleroderma and healthy subjects. We hypothesize that scleroderma fibroblasts will express increased interferon regulatory factor 7 (IRF7) compared to normal fibroblasts. The experiment was designed using two dermal fibroblast cell lines each from normal subjects and scleroderma subjects. Cells were stimulated with either BSA, TGF beta or IFN alpha-2 for 24 hours. BSA and TGF beta were controls. Total RNA was harvested, QRT-PCR was performed, and fold change was calculated. In scleroderma fibroblasts, the IRF7 fold change in response to interferon alpha was 6.92. Normal fibroblasts had an IRF7 fold change of 3.33. These results support the hypothesis. The data suggests a link between IFN and skin fibrosis in scleroderma. IFN may regulate dermal fibroblast function.

ABSTRACT

Wnt5b binding to Fzd5 in endometrial cancer cells

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Sponsored by: David S. Loose, PhD, Department of Integrative Biology and Pharmacology

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

Key Words: Endometrium, wnt5b, Fzd5, SFRP1

One of the molecular causes of endometrial cancer is dysregulation in the wnt signaling pathway. Wnts are ligands which bind to specific plasma membrane receptors. The action of some wnts is an increase in nuclear β -catenin. Nuclear β -catenin acts as a transcription factor and increases the transcription rate of specific genes, many of which control the cell cycle. In human endometrium, wnt3a binds to frizzled receptor Fzd5. Wnt5b, another endometrial ligand, is 45% similar in its protein sequence to wnt3a and is located on a different chromosome. Our hypothesis is that wnt5b will bind to Fzd5, similar to wnt3a. To test this hypothesis, the endometrial cancer cells were transfected with Fzd5 and treated with both wnt3a and wnt5b. Using a luciferase reporter system, which acts as a readout of active β -catenin, we compared the effects of wnt3a and wnt5b on Fzd5 signaling. The results show that wnt5b acts as an antagonist, independent of Fzd5. Comparing relative luciferase activity levels, Fzd5 interacts with wnt3a to a much greater extent than with wnt5b.

Alongside comparing wnt5b to wnt3a, we are working with secreted frizzled related proteins, SFRPs, molecular antagonists that bind to wnts. SFRP4 binds wnt7a and prevents its binding to Fzd5. SFRP1 is another protein that is not yet functionally characterized. Our prediction is that, compared to SFRP4, SFRP1 will bind to a different set of wnt proteins and antagonize their activity.

ABSTRACT

Reinforcing Effects of Ethanol in Rats: Concurrent Fixed-Ratio Schedules

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

Key Words: drug self-administration, concurrent fixed-ratio schedule, ethanol, reinforcing
effects, preference

Alcohol can become a reward or reinforcer when consumed by animals, including humans. The object of this study was to assess the relation between ethanol dose and reinforcing effects by way of oral self administration in rats by testing a range of concentrations using both sequential and concurrent presentation of ethanol concentrations. Seven male Long Evans rats were trained to respond on a fixed-ratio 8 reinforcement schedule in chambers equipped with two identical fountain self-administration devices, and were presented with various concentrations of ethanol (2%, 8%, 32% *w/v*) or a water vehicle in daily three hour sessions with the rats having a choice to respond to either device or not to respond at all. The concentration of ethanol was varied across sessions in an ascending-descending sequence for twelve conditions to control for and detect sequence effects and changes in behavior over time. The preliminary results for one rat show that the higher concentrations of ethanol were generally preferred, i.e. maintained a higher mean for responding than concurrently available concentrations of 8% or less and water in spite of the finding that 8% ethanol produced the highest absolute response rats when concentrations were presented sequentially. These results indicate that higher concentrations of ethanol (32%) produce the most reinforcing effects and that concurrent choice methods can be used to measure such effects.

ABSTRACT

Effects of Ethanol on *fox2* Mutants in *Candida Albicans*

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Sponsored by:	Mike Lorenz, PhD, Department of Microbiology and Molecular genetics	
Supported by:	The University of Texas at Houston Medical School - Summer Research Program	
Key Words:	<i>Candida Albicans</i> , alternative carbon metabolism	

Candida albicans is the most important fungal pathogen of humans, mostly affecting patients with defects in innate immunity. *C. albicans* has been shown to induce alternative carbon metabolism pathways during stress situations, such as during contact with macrophages, a phagocyte of the innate immune system. One alternative pathway, β -oxidation, has been shown to be necessary for full virulence in mouse models. *Candida albicans fox2* mutants do not grow on ethanol as a carbon source, unlike *Saccharomyces cerevisiae fox2* mutants. We asked whether the *C. albicans fox2* strain could not grow on ethanol or were being killed by this stress. To test this, *C. albicans* wild-type or *fox2* deletion strains were grown in both glucose and ethanol and survival was measured by plating for colony forming units (CFUs) at various time intervals. Both strains grew at a similar rate in glucose, while in ethanol the wild type had slower growth rates and *fox2* did not grow. Based on this study ethanol is not toxic for *fox2* mutants, just arrests further growth. This work has contributed to our further understanding of the *C. albicans fox2* deletion strain, and reinforced the differences in carbon metabolism in *C. albicans* when compared with *S. cerevisiae*.

ABSTRACT

Listeria Monocytogens

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Sponsored by: Dr. Rick Wetsel, Institute of Molecular Medicine

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

Key Words: Carboxypeptidase, C5a receptor, monocytogenes

Listeria monocytogenes is a Gram-positive bacterium found in contaminated foods with a natural route of infection through the gastrointestinal tract. Following infection, a rapid innate immune response is crucial for host survival making this bacterium a useful tool in examining the functions of innate immunity in mouse models. Previous studies have shown that Carboxypeptidase N (CPN) is able to cleave basic amino acids and inactivate the complement anaphylatoxins C3a and C5a. These anaphylatoxins act as pro-inflammatory mediators for local inflammatory processes. The C5a receptor plays an important role in the pathogenesis of many inflammatory diseases as well as recruiting phagocytes for microbial clearance. In this study, C57BL/6, CPN *-/-* and C5aR *-/-* mice were infected with *L. monocytogenes* via intravenous, intraperitoneal and orogavage inoculation and the relative susceptibility of each was analyzed. The results showed that both the CPN *-/-* and C5aR *-/-* mice, when compared to wild-types, did not differ in the bacterial burden in spleens and livers. Upon examining IL-1B and IL-6 spleen and serum homogenate, there was no difference in production of these cytokines. These findings suggest that previous reports of increased susceptibility to *L. monocytogenes* infection in A/J mice is likely not due to their C5-deficiency.

ABSTRACT

Antiretroviral Therapy-The viralogic efficacy and safety

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Sponsored by: Dr. Philip C. Johnson, Robin Hardwicke PhD, FNP

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

Key Words: NEwaArT, Nerirapine vs. Atazanavir, Anti-retro viral therapy

Human immunodeficiency virus (HIV) the precursor for acquired immunodeficiency disorder (AIDS) is part of the retroviral family. The treatment for HIV/AIDS is delivered through antiretroviral medication therapy. The objective was to identify a patient that fit the inclusion criteria: CD4 count of <400 celles/mm³, Krnofsky score of ≥ 70 , no prior NRTI or nNRTI (naïve), 18 years of age or older.

This is an open-label, randomized clinical study to compare the viralogic efficacy and safety of two separate regiments of antiretroviral medications. The study will randomizes the patient to a combination of a non-nucleoside analog reverse transcriptase inhibitor (nNRTI), boosted with a protease inhibitor (PI) and Truvada or a nucleoside analog reverse transcriptase inhibitor (NRTI) boosted with a PI and Truvada.

Before identifying starting the study a site initiation was conducted to ensure that all involved comprehend the protocol. Once identified, the patient was screened to determine if appropriate for the study, before enrolling the patient in the study. The greatest part of this program was spent in clinics and the hospital trying to identify a candidate for the study. Two patients were identified, one was screen and the other has yet to be screened. Once the results are delivered the enrollment could be initiated.

Due to the design of the study, the enrollment period is anticipated to span over the next calendar year prolonging the forthcoming of a conclusion.

ABSTRACT

Tracheal Stenosis in Burn Patients

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

Key Words: tracheal stenosis, burns

Tracheal stenosis is a rare, but potentially serious complication of burn injuries. It is commonly associated with internal trauma caused by prolonged intubation. Tracheal stenosis is usually delayed, with onset of symptoms being weeks or months after initial injury. Patients may present with dyspnea, stridor, and hoarseness. The purpose of this study was to evaluate the characteristics of tracheal stenosis in the burn population.

A retrospective chart review was performed. Patients were identified by surgical faculty, and a cross reference of specific CPT codes. A datasheet was developed to summarize relevant information. It was organized into subcategories: demographics, burn information, airway injury and management, stenosis details, and treatment.

Ten burn patients with tracheal stenosis have been identified. There was one female and nine males. The average patient age was 39 years. Seven patients' burns were flash or flame in origin. Two patients received inhalation injuries. Six patients had head and neck burns. All were large burns (average burn size was 46%, ranging from 35%-70%), which is consistent with the population requiring prolonged intubation. All patients were intubated on admission to the hospital. The average intubation time was 30 days. All patients evaluated at this point have required tracheostomy to achieve an adequate airway. These patients required additional procedures, and laser dilation was the most common specific treatment modality. Mitomycin application was favored following laser dilation.

These results reinforce our practice of closely monitoring burn patients with prolonged intubation for airway difficulties. The investigation is ongoing.

ABSTRACT

Characterization of the interaction between Ku70/Ku80 and Net1

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Sponsored by: Jeffrey A Frost PhD Integrative Biology and Pharmacology

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

Key Words: Ku70, Ku80, Net1, DNA damage, ionizing radiation

Ku70 and Ku80 are scaffolding proteins required for double strand DNA break repair within cells. They also have roles in other regulatory processes, such as ubiquitylation and apoptosis. Previous work indicated that both Ku70 and Ku80 interacted in vitro with the C-terminus of the RhoGEF Net1 (neuroepithelioma transforming gene 1). This was significant because Net1 was recently shown to regulate cell survival in response to DNA damage. Thus, the identification of Ku70/Ku80 as Net1 interacting proteins may serve as the mechanism by which Net1 protects cells from DNA damage induced apoptosis. To confirm that full length Net1 and Ku70/Ku80 interact in cells, we examined whether these proteins co-immunoprecipitated from Hela cells. Importantly, we observed that both endogenous and overexpressed Net1 and Net1A interacted with endogenous Ku70 and Ku80. To test whether this interaction was modulated by agents that damage genomic DNA, Hela cells were exposed to UV light, ionizing radiation or doxorubicin for different periods of time, and then the interaction between Net1 and Ku70/Ku80 was examined. These agents were chosen because they cause DNA crosslinks, DNA double strand breaks, or intercalate within the DNA strand, respectively, and thereby elicit distinct cell responses. Preliminary studies showed that there was no change in the binding between Ku proteins and Net1 over a 24 hour period following treatment with UV or doxorubicin. However, binding between Net1 and Ku70 or Ku80 appeared to increase following treatment with ionizing radiation. Thus, these results indicate that double strand DNA breaks, but not other forms of DNA damage, modulate the interaction between Net1 and Ku70/Ku80. Furthermore, these results suggest that this interaction may be important for the response of cells to this form of DNA damage.

ABSTRACT

Validation and Development of Pre-Hospital Triage Algorithms

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Sponsored by: Rosemary A. Kozar, MD, PhD

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

Key Words: triage, mortality, blood pressure

The objective of the current study was to assess the accuracy of two triage algorithms in predicting civilian mortality in a non mass casualty setting. A total of 244 injured patients arriving to Memorial-Hermann Hospital via Life Flight were analyzed. Ages ranged from 18-86 years, mechanisms were 214 blunt and 29 penetrating traumas, and were among 180 males and 63 females. The number of criteria met by two mass casualty scoring systems was calculated. The newly proposed American College of Surgeons-Field Triage Disaster (ACS-FTD) score evaluates patients by Glasgow Coma Score (GCS) ≥ 14 , systolic blood pressure ≥ 90 and respiratory rate (RR) >25 while the commonly used START Adult Triage mass casualty algorithm uses RR >30 , normal perfusion, and mental status (obeys commands). As shown in

# criteria met	MORTALITY (%)	
	ACS-FTD	START
0	100	100
1	13.3	42.9
2	7.4	11.1
3	0	2.0

the table, if patients failed to meet any of the proposed criteria using either scoring system, there was a 100% mortality. In conclusion, these data suggest that simple scoring systems can accurately predict mortality in a busy urban Level I trauma center. Such data may

prove valuable even in non mass casualty situations in appropriately utilizing health care resources. Larger studies to validate these findings are warranted.

ABSTRACT

Does orientation discrimination show a bias consistent with an internal model of gravity?

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Sponsored by: Valentin Dragoi, PhD, Department of Neurobiology and Anatomy

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

Key Words: Psychophysics, orientation discrimination, gravity, visual perception

Current psychophysical and physiological research suggests that neural processing incorporates a model representation of physical laws. Could such a model involving higher cognitive processes affect early visual perception? The purpose of this study was to test whether orientation discrimination showed a bias for orientation lines decreasing in angle toward the horizontal plane. Such a bias could then be due to the visual statistics of an object moving down by gravity. Participants viewed pairs of orientation gratings that were successively flashed at a fixed location in retinal periphery. Phase of the gratings changed for half of the trials, and there was a delay between the two gratings to rule out any other cue besides orientation. The first grating appeared at a 45 degree angle from horizontal, while the second grating was flashed at a decreased, increased, or unchanged angle with respect to the first. After the second grating was presented, participants indicated whether the angle orientation increased or decreased while degree thresholds were calculated using the staircase procedure. Better discrimination performance was observed for angles moving toward the vertical plane ($p < 0.05$, paired t -test), demonstrating that orientation discrimination performance does not show the influence of an internal model complying with the visual statistics of movement due to gravity. Further studies should test why this particular bias in perception occurs, if not due to gravity, and whether it persists when other manipulations are made to the presentation of the stimuli.

ABSTRACT

The Role of Dietary nucleotides on Mesenteric ischemia/reperfusion injury

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

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

Key Words: Surgery, Ischemia, Reperfusion, RNA, Nucleotides, Mesentery, Edema, Mice.

Intestinal ischemia/reperfusion (I/R) injury is a common problem in trauma medicine. I/R play a critical role in the pathogenesis of post injury multiple organ failure (MOF) with a high index of mortality. Research in animals has found that Nucleotide supplements are important in protein synthesis and the repair mechanism of immune cells. Under ischemic conditions, protein synthesis may not be rapid enough to meet the body's requirements for tissue repair and immune function. We hypothesized that exogenous nucleotide supply may optimize polypeptide synthesis, leading to normal repair function of the gastrointestinal and immune systems during recovery from mucosal injuries.

Male ICR mice were fed either control chow or RNA supplemented chow for two weeks. Mice were divided into two groups, sham group, and superior mesentery artery occlusion (SMAO) group. SMAO group underwent 45 min. ischemia, and 30 min. or 6 hrs. reperfusion. Organs were removed for histological examination using H&E staining and apoptotic assays by tunnel staining. Tissue was also measured to assess edema by wet/dry ratio.

With control diet, SMAO caused severe mucosal injury (disintegration of lamina propria, hemorrhage and ulceration) in ileum (Chiu score 4 ± 0.4 30 min. & 2.8 ± 0.5 60 hrs) and jejunum (3.1 ± 0.3 30 min. & 4.1 ± 0.4 6 hrs). RNA diet maintained the mucosal architecture and significantly decreased the SMAO induced mucosal injury in ileum (2.8 ± 0.6 30 min. & 2 ± 0.3 6hrs) and jejunum (2.4 ± 0.5 30 min. & 1.8 ± 0.3 6hrs). RNA also decreased tissue edema compared to control diet in ileum and jejunum, no clear difference in liver. Sham group also reflected similar results on ileum (Control 2.6 ± 0.4 / RNA 0.3 ± 0.4), and jejunum (Control 2.6 ± 1 / RNA 1 ± 0.7). Lung biopsies had less end-organ injury and neutrophil infiltration in RNA group than that in control group. Tunnel assays showed similar improvements in apoptotic events in tissues.

Although under normal conditions, dietary nucleotide supplementation is not considered to be essential for support and growth. After I/R injury, RNA dietary supplementation shows improvement in ileum and jejunum tissue. Our results suggest a new application to decrease significantly I/R organ injury in trauma patients with high risk for MOF. Further studies will clarify the mechanism.

ABSTRACT

AKAP150 Expressed in a Range of Nociceptive DRG Neurons

BRIAN GILCREASE-GARCIA

Rice University

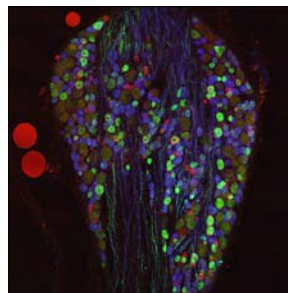
Class of 2010

Sponsored by: Raymond J. Grill, Ph.D., Department of Neurosurgery

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

Key Words: neuropathic pain, spinal cord, PKA, cAMP

Neuropathic pain is a common ramification of peripheral and spinal cord injury. Following injury, pain neurons in nociceptive pathways often exhibit spontaneous activity and abnormal sensitivity due to natural inflammatory response (Ji, Suter, *Molecular Pain* 3.33, 2007). Thus, in a dichotomous effort to repair neurological damage, the body may cause a neuropathic pain syndrome while attempting to rehabilitate the nervous system. cAMP is a secondary messenger that promotes neuroregeneration following injury (Neumann, Bradke, Tessier-Lavigne, Basbaum, *Neuron* 34.6, 2002). A-kinase anchoring proteins (AKAPs) are a family of intracellular scaffolding proteins that regulate and compartmentalize cAMP signaling. AKAP150 is expressed by nociceptive neurons of the dorsal root ganglion (DRG). This AKAP isoform is thought to be important in the generation of thermal hypersensitivity resulting from inflammation. The purpose of this study is to identify subpopulations of nociceptive DRG sensory neurons that express AKAP150. We performed an immunohistochemical analysis of AKAP150 expression within both the lumbar DRG and spinal cord. Epifluorescence digital imaging and confocal microscopy were used to assess AKAP150 association with the nociceptive markers CGRP and IB4.



Imaging revealed three subpopulations of nociceptive neurons in the DRG, based on co-localization of fluorescent markers: 1) IB4+/CGRP+/AKAP150+; 2) IB4-/CGRP+/AKAP150+; and 3) IB4-/CGRP+/AKAP150-. Primary afferent input to the dorsal horn demonstrated a similar labeling pattern. This study shows a significant number of nociceptive neurons in both the dorsal horn and DRG that express AKAP150. Future research will examine the effects of disrupting AKAP150 function in nociceptive nerves to inhibit the development of neuropathic pain.

ABSTRACT

Assessing the Content, Presentation, and Readability of Dental Informed Consents

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Sponsored by: Muhammad Walji, PhD, Department of Diagnostic Sciences

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

Key Words: Informed consent, dental, readability, layout

Informed consents for treatments and procedures are important aids in helping patients make optimal decisions. However, analyses of informed consents in medicine suggest that these documents are often incomplete, difficult to navigate, and require high reading levels. Little knowledge exists about the quality of dental informed consents. The objective of this study was to assess the quality of informed consents at the University of Texas Dental Branch. Fifty-two consents (31 clinical and 21 non-clinical) were rated using a content criteria instrument adapted from Bottrell *et al.* (2000) and presentation criteria from the Suitability Assessment of Materials (SAM) instrument. Readability measures used in the analyses included Flesch Reading Ease, Flesch-Kincaid grade level, and Simple Measure of Gobbledygook (SMOG). Of the clinical consents, 26 % of forms contained all four of the basic content elements (description of procedure, risk, benefits, and alternatives), 48% contained 3 of 4 elements, 16% contained 2 of 4 elements, and 10% contained 1 of 4 elements. The average clinical consent had 7 items out of the selected 12 layout items present, and the average nonclinical consent had 8 items out of 12 items (some of which include bulleted text and type size). Average Flesch-Kincaid grade level was 12.7 (range, 7.4-19.1), significantly higher than the recommended eighth grade level ($p=3 \times 10^{-17}$). The results suggest that many existing dental informed consents may be improved by 1) increasing the comprehensiveness of the content, 2) improving the design and layout and 3) reducing the reading levels for patient comprehension.

ABSTRACT

Detection Of Potential Causative Agent Of Southern Tick-Associated Rash Illness By PCR

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Sam Houston State University

Class of 2011

Sponsored by: Steven J. Norris, Ph.D, Dept. of Pathology & Laboratory Medicine

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

Key Words: STARI, Causative Agent, Detection

Lyme disease or Lyme borreliosis (LB) is the most prevalent tick - borne disease in the U.S. More than 80% of LB cases in the U.S. occur in the northeastern, north central, mid - Atlantic seaboard, and Pacific coastal states. However, illnesses consistent with LB have been reported in Texas and the south central U.S. Because the causative agent has not been isolated from patients in this region, the term "Southern Tick - Associated Rash Illness" (STARI) was recently introduced by the CDC to describe this syndrome. Several lines of evidence indicate the occurrence of some form of Lyme borreliosis in this region, however, to date no one has been able to identify, characterize, or culture *Borrelia* organisms associated with STARI/Lyme-like illness in Texas or nearby states. The latest evidence indicates that LB and STARI have distinct clinical presentations, and that LB serologic tests are nonreactive in STARI patients. The etiology of STARI thus remains unknown. Forty skin specimens from STARI patients in Missouri have been screened by using 3 pairs of primers targeted 16S rRNA gene (*B. burgdorferi*-specific primers, *Borrelia* species-specific primers, and degenerate primers for bacteria) and 1 pair of *Borrelia* species specific primers for *flaB* gene. Of the 40 skin samples, 8 showed positive result in 16S rRNA gene and 12 positive results were observed in *flaB* gene. Sequence and phylogenetic analysis will be performed to confirm PCR result and define the species/genospecies of these putative pathogens.

ABSTRACT

Increased Risk for Executive Dysfunction in Children Expressing ADHD Symptomatology, Not Autistic Symptomatology.

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Sponsored by: Deborah A. Pearson, PhD,

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

Key Words: autism, ADHD, executive function

The purpose of this study was to explore the possible correlations between parent ratings of severity of ADHD and autistic symptomatology and the severity of adverse effects of ADHD and autism symptomatology on executive function (EF). Subject screening yielded a sample of 67 children (55 boys, mean age = 9.3 yrs, mean IQ = 80.7) who, through ADI-R and ADOS questionnaire testing, met the DSM-IV requirements for autism. The SCQ, SNAP-IV and BREIF questionnaires done by parents were used to assess, respectively, autistic symptomatology, ADHD symptomatology, and executive functioning. A direct, positive correlation was found between severity of ADHD symptomatology and EF deficits. These two findings suggest that when compared to autistic children who experience little or no ADHD symptomatology, children with autism who do express significant ADHD symptomatology are at greater susceptibility to executive functioning deficits.

ABSTRACT

The Role of the Caudate Nucleus on the Acute and Chronic effects of MPD (Ritalin)

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Sponsored by: Dr. Nachum Dafny, PhD, Department of Neurobiology and Anatomy, Dr. Alan Swann, MD, Department of Psychiatry and Behavioral Sciences

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

Key Words: Behavioral sensitization; Methylphenidate; Caudate Nucleus; Acute and chronic treatment; Withdrawal

Methylphenidate (MPD), known by its familiar name Ritalin, is a stimulant drug used extensively in the treatment of hyperkinetic children suffering from Attention Deficit Hyperactivity Disorder (ADHD). ADHD patients treated with MPD for prolonged periods of time can cause adverse affects such as dependency. MPD action occurs in the neuronal circuit known as the motive circuit, by binding to dopamine (DA) transporters; it causes an accumulation of dopamine in the synaptic space.

The aim of this study was in investigate the role of a specific component of the motive circuit, the Caudate Nucleus, and the effects of acute and chronic MPD administration, using the open field assay and adult male Sprague-Dawley rats with bilateral electrolytic lesions of the Caudate Nucleus were used. On the first day following a saline injection all animals were recorded establishing baseline. Ensuing baseline, animals were divided into three groups, (1) an intact control group (N=8), (2) a sham operational group (N=5), and (3) a lesion group (N=6). Groups 2 and 3 underwent surgery and allowed 5 days recovery. Following recovery, recordings were resumed for 11 days as follows: 1st day post surgery a saline injection was given, followed with six consecutive daily injections of 2.5 mg/kg MPD, 3 days of washout period and another re-challenge of 2.5 mg/kg MPD. Each recording lasted 2 hours post injection.

Acute MPD treatment elicits similar increases in locomotion in all three animal groups. Data collection concerning the role of chronic MPD at the Caudate Nucleus such as sensitization and tolerance is ongoing and long term effects are not yet known.

ABSTRACT

Type IV Secretion System

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Sponsored by: Christie, Peter J., PhD.

Supported by: The University of Texas at Houston Medical School - Summer Research Program
Molecular Basis of Infectious Diseases (MBID) Trainee Grant

Key Words: Type IV Secretion System, VirB2

Type IV secretion systems (T4SSs) are trans-membrane, multi-subunit complexes that trace their ancestral roots back to bacterial conjugation systems. A broad range of both gram-positive and -negative bacteria utilize the T4SS to transfer DNA and/or protein(s) into prokaryotic or eukaryotic cells. The *Agrobacterium tumefaciens* VirB/D4 T4SS mediates the transfer of single-stranded DNA and protein virulence factors into plant cells, leading to the formation of Crown Gall tumors. The VirB/D4 T4SS consists of twelve protein subunits (VirB1-VirB11 and VirD4), which assemble to form a secretion channel spanning the cell envelope and an extracellular T-pilus. In *A.tumefaciens*, VirB2 is an essential component of the secretion channel and the major subunit of the T-pilus. At present, there is no structural information for cellular associated VirB2 or the extracellular T-pilus. Single cysteine substitution mutants made along the length of VirB2 were tested in vivo for oxidative cross-linking to begin to define elements of VirB2 conformation. Disulfide cross-linking demonstrated that VirB2 is dynamic, involving changes in cross-linking seen in the cellular associated VirB2 and the T-pilus. Dimerization of VirB2 proteins occurs at cysteines 67 (TM1), 71 (TM1), 94 (TM2), and 107 (TM2). This suggests that there is close contact between VirB2 subunits within the hydrophobic regions TM1 and TM2. Crosslinking in the TM1 region of T-pilus VirB2 occurs at points that are important for pilus stability (64, 67, 77, and 83). The combined results of cellular and extracellular VirB2 shows that crosslinking occurs in both TM1 and TM2 regions in the cellular form while the pilus VirB2 makes contacts only in the surface exposed TM1 region.

ABSTRACT

Tie-1 and SM22 Promoters in Differentiated Embryonic Stem Cells

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Sponsored by: Yong-Jian Geng MD, PhD, Department of Internal Medicine

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

Key Words: Embryonic stem cells, pECFP, pEYFP, SM22, Tie-1

Embryonic stem cells (ESC) have been proposed to have many medical applications involving the repair or the replacement of a wide range of specialized cells. ESCs have the ability to differentiate into almost any kind of cells in the body. Because of their carcinogenic properties, the direct use of these stem cells has been a continuous problem. Therefore, more research has to be conducted to identify specialized cells produced from differentiated ESCs before any therapeutic avenues become a reality. To identify endothelial and smooth muscle from differentiated ESCs, we cloned the cDNA sequences corresponding to the human promoter sequence of Tie-1, an endothelial specific receptor tyrosine kinase, and of SM22, an actin binding protein in smooth muscle cells, into two plasmids encoding two different fluorescent proteins, pEYFP and pECFP, respectively. Both of these promoters are activated only in their respective differentiated cell types and hence will fluoresce. ESCs, were transfected with pEYFP/Tie-1 and pECFP/SM22 and cultured in the presence of geneticin, an antibiotic killing only the cells that do not harbor the plasmids, stable colonies were isolated, differentiated, and fluorescence was observed under a fluorescent microscope. Human aortic endothelial cells (hAEC) and vascular smooth muscle cells (VSMC) were used as positive controls. We observed that differentiated ESCs were positive for both SM22 and Tie-1 activation after 10-12 days in culture.

ABSTRACT

HPV Typing in Lesions from Patients with WHIM Syndrome

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

Key Words: WHIM syndrome, HPV, CXCR4, HPV-6

The WHIM syndrome (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) is a dominant autosomal rare immunodeficiency disorder. WHIM syndrome can be caused by mutations in CXCR4, a chemokine receptor gene, or by a dysfunction in GRK3. It is most commonly characterized by neutropenia, extensive human papillomavirus (HPV) infections, and hypogammaglobulinemia. No specific HPV typing has currently been reported; therefore the aim is to determine which HPV types are more closely related with WHIM syndrome. A biopsy of genital and acral verrucae from a patient carrying a R334X mutation on the CXCR4 gene was received for HPV typing. DNA extraction was performed followed by nested PCR with consensus primers to detect different groups of HPV. To detect anogenital HPV, PGMY-GP+ sets of consensus primers were used. To detect epidermodysplasia verruciformis (EV), EV-HPV consensus primers were used to detect the other HPV families. Amplifiable DNA quality was assured by performing PCR using beta-globin. Putative anogenital HPV products detected by agarose gel electrophoresis was purified, cloned, and sequenced. By comparing the obtained sequences with the NCBI Gen Bank using Blast search tool, HPV-6 was verified in the DNA sample from the penile shaft. This is the first report of HPV typing in patients with WHIM syndrome.

ABSTRACT

Title: Improving the efficacy of BCG vaccine against tuberculosis

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Sponsored by: Robert L. Hunter, MD, PhD., Department of Pathology and Laboratory Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program, Dr. Douglas Kernodle, Vanderbilt University

Key Words: BCG vaccine, Antigen presentation, Macrophage, Tuberculosis

Tuberculosis is the leading cause of death by infection. *Bacille Calmette Guerin* (BCG) is a live vaccine that has been used for prevention, but is largely ineffective. However, newer vaccine trials with a BCG knockout of the superoxide dismutase gene (SOD-KO) show increased efficacy. The mechanism of SOD-KO is poorly understood, and is explored in this study. BCG hides within macrophage phagosomes, and evades immune recognition important for long term immunity. We speculated that the SOD enzyme secreted by BCG renders the phagosomal compartment in macrophages alkaline by breaking down oxidants. We proposed that this in turn prevents antigen presentation by proteolysis, and consequently T cell recognition. To test these hypotheses, mouse macrophages were infected with wild type BCG (wt-BCG) vaccine and the SOD-KO. Macrophages were then overlaid with T cells specific for peptide Ag85B. When BCG-infected macrophages present Ag85B, it is recognized by T cells that secrete IL-2. IL-2 levels were determined using ELISA. The wt-BCG induced less IL-2 (< 200 pgs/ml) in macrophages while the SOD-KO strain induced > 500 pgs of IL-2/mL ($p < 0.004$, t test). SOD-KO mutant was thus more antigenic in macrophages than wt-BCG. Inhibition of oxidants with diphenyliodonium chloride (DPI) enhanced the growth of SOD-KO in macrophage cultures. This suggested that macrophage oxidants normally kill BCG, facilitating antigen production. However, BCG derived SOD prevents killing, enhances survival and reduces antigen production and immunogenicity. We propose that genetic manipulation of BCG is an attractive strategy for improving its efficacy by removing genes that disrupt antigen-processing and presentation.

ABSTRACT

Evaluation of the Effect of Tobramycin on *Staphylococcus aureus* Biofilm Formation

PATRICE N LOVE

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Sponsored by: Heidi Kaplan, PhD, Department of Microbiology

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

Key Words: *Staphylococcus aureus*, biofilms, tobramycin, osteomyelitis

Total joint replacement surgeries have a 2% incidence of infection in the roughly 600,000 cases performed annually in the U.S. *Staphylococcus aureus* is the major cause of these osteomyelitis infections, due to its ability to grow on surfaces including orthopedic biomaterials. A biologically active population of microorganisms that is attached to a surface and encased by an extracellular matrix is termed a biofilm. Biofilm-grown *S. aureus* are more resistant to antimicrobials than planktonic cells, making the treatment and eradication of biofilms difficult. Polymethylmethacrylate (PMMA) bone cement with and without tobramycin were formed into discs and used as a growth substrate in an *in vitro* model for *S. aureus* osteomyelitis biofilm infections to evaluate the effectiveness of tobramycin in inhibiting biofilm formation. The *S. aureus* biofilms were grown on the discs in 24-wells culture dishes with synthetic synovial fluid (SSF). The discs were incubated at 37°C and the SSF was changed daily. The biofilms were stained with fluorescent Live/Dead BacLight stain, and viewed using a laser scanning confocal microscope on days 3, 4, and 5. The nPhlip2.0 computer program analyzed several parameters (biovolume, substratum coverage, and thickness). The results indicate that although biofilms grew on both discs, the biofilms were more substantial on the PMMA discs without tobramycin. Thus, PMMA with tobramycin does inhibit *S. aureus* biofilms formation at the initial stage of biofilm growth. However, by 5 days of incubation the effect of tobramycin appears to be greatly reduced due to a measured loss of antibiotic from the discs.

ABSTRACT

HPV DNA in Transitional Cell Carcinoma from the Nasolacrimal Duct

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

NIH sponsored Molecular Basis of Infectious Disease Training Grant Program

Key Words: Transitional Cell Carcinoma, HPV, PCR, sinonasal tract, nasolacrimal duct

Transitional cell carcinoma (TCC) originates from the transitional epithelium of organs capable of adjusting to fluctuating volumes of fluid. One area targeted by TCC is the nasolacrimal duct of the sinonasal tract. Although the role of Human papillomavirus (HPV) DNA in the development of TCC is controversial, some tumor tissues harbor HPV DNA.

A paraffin-embedded TCC sample from the sinonasal tract was utilized to find HPV DNA. DNA was extracted from the tissue and the Polymerase Chain Reaction (PCR) method was applied. The beta globin reference gene PCR results proved that the sample had an amplifiable quality of DNA. The DNA sample was tested using nested PCR with the PGM1/GP+ primer set system. After NuSieve/LE 3:1 agarose gel electrophoresis of the second PCR (GP+) assay, a 150 bp putative HPV PCR fragment was extracted and cloned using the TOPO-TA cloning system. Nine bacterial colonies were picked up from the agar plate for plasmid propagation. The plasmid propagations proved successful and were sent for sequencing using the M13 Reverse priming site of pCR 4- TOPO vector. The sequencing results revealed the presence of HPV 11 DNA.

Previous studies have shown a high incidence of infection with HPV 6 and HPV 11 in TCCs from nasolacrimal duct. Our result confirms the presence of HPV 11 infection in TCC with nasolacrimal origin. This finding supports the theory that HPV type 11 may play a role in the development of TCC.

ABSTRACT

Analysis and Improvement of SETTRAC Stroke Committee Policies

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Sponsored by: Dr. James C. Grotta, MD, Department of Neurology

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

Key Words: SETTRAC, stroke, tPA

The SETTRAC stroke committee was formed to improve regional stroke care through coordination and education of designated stroke centers.

Purpose: To increase the scope of the SETTRAC Stroke Committee through policy review.

Methods: We drafted a confidentiality statement to ensure participating hospitals of privacy policies. We revised the data form to be shorter detailing only core measures. We called every SETTRAC hospital to update contacts and initiate feedback. We alerted non-SETTRAC hospitals of the pending certification process. We used the Texas Health and Safety Code as a source for sanctions against noncompliance. Finally, we began planning a SETTRAC representatives and hospitals event to facilitate discussion among members.

Results: The committee decided that all documents should be reviewed by legal counsel. It accepted the revised data form. A comprehensive spreadsheet of SETTRAC contacts was created, and 22 hospitals agreed to be stroke centers. Data is being collected on patients transported to and treated by stroke centers. Members felt that the role of the committee does not involve sanctioning, but should respond to noncompliance with review and education. A subcommittee was established to suggest reviewing policies. Plans for the SETTRAC party continue.

Conclusion: The SETTRAC Stroke Committee can extend its influence in the region after policy review. The future of these policies requires outside council as well as internal agreement. By improving communication among members through contact information, sharing events, and the creation of known policies, the committee is forming a solid foundation for regional treatment improvement.

ABSTRACT

NEwArT Clinical Trial for more effective treatment of Human Immunodeficiency Virus

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Sponsored by: Philip Johnson, MD; Robin Hardwicke, PHD, NP-C

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

Key Words: Human Immunodeficiency Virus, HAART, Antiretroviral Treatment

Human Immunodeficiency Virus is a retrovirus that targets CD4 Cells as self-replication sites, and therefore greatly compromises infected patients' immune systems. An HIV positive individual can progress to having AIDS, which is characterized by the presence of an opportunistic infection or CD4 count less than 200. Since 1998, standard treatment of HIV has been Highly Active Antiretroviral Therapy (HARRT), which includes combo therapy utilizing drugs that target several stages of the HIV replication process. Increases in diagnostic technologies and pharmaceutical advances have led to highly effective management of the infection. Because of this, treatment guidelines improve frequently. The present study examines the difference between nevirapine and atazanivir boosted with ritonavir on a background of tenofovir and emtricitabine on a two year timeline. 150 patients are requested by Boehringer Ingelheim for the study. This period of time was used to find and introduce patients to the study, and to screen them for any exclusion criteria.

So far, three patients have been found for study, and one has been screened fully. Inclusion criteria included but are not limited to patients who: give informed consent, are 18 y/o or greater, had no prior antiretroviral treatment for more than 10 days, and who have a CD4 count lower than 400 cells/mm³. Exclusion criteria include, but are not limited to history of drug abuse, a history of hepatitis, or a history of any AIDS defining illness. Study evaluators were present at the start of the study as well as at the clinic after the first patient went through the screening process. This was to ensure that all guidelines and standardizations were being adhered to. Because of the nature of the study, there have not yet been any definitive conclusions drawn as to which regimen is more effective to manage HIV.

ABSTRACT

Intestinal ischemia/reperfusion & multiple organ failure

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Sponsored by: Anil Kulkarni, MSC PhD, Department of Surgery

Supported by: Dr. Kulkarni's grant, Dept. of Surgery, and The University of Texas at Houston Medical School - Summer Research Program

Key Words: Ischemia, reperfusion, AHCC, Active hexose correlated compound, Mice, SMAO

Intestinal ischemia/reperfusion (I/R) injury is a common problem in critical trauma & medicine and plays a crucial role in the pathogenesis of post injury multiple organ failure (MOF) with a high index of mortality. Previous experimental studies have demonstrated that a fermented mushroom extract- active hexose correlated compound (AHCC), has immunomodulatory effects in pre-clinical studies. AHCC has also been known to improve health in humans. This study investigates the effects of an AHCC diet on the I/R model with respect to health and recovery of the affected tissue. Male ICR mice were fed either control chow or chow supplemented with AHCC (0.4%) diets for two weeks. The mice were then randomized into two groups: Sham Group with laparotomy only and SMAO group with superior mesentery artery occlusion (SMAO) for 45 minutes and 6 hours reperfusion. With control diet, SMAO caused severe mucosal injury (disintegration of lamina propria, hemorrhage and ulceration) in ileum and jejunum (Chiu score 3.9 ± 0.6 & 3.7 ± 0.4 , respectively). AHCC diet maintained the mucosal architecture and significantly decreased the SMAO induced mucosal injury in ileum and jejunum (Chiu scores 2.1 ± 0.4 & 2.5 ± 0.5 , respectively). Lung biopsies had less end-organ injury and neutrophil infiltration in AHCC group than that in control group. AHCC also decreased tissue edema as a result of I/R injury (>66%) compared to control diet in ileum>lung>jejunum, no difference in livers. Tunnel assays showed similar improvements in apoptotic events in tissues. AHCC dietary supplementation provides significant protective effects against mucosal I/R injury, and SMAO-induced remote organ injury. Our results suggest a new application to inhibit I/R organ injury in trauma patients at high risk for MOF. Further studies will clarify the mechanism.

ABSTRACT

Detection of the lipopolysaccharide (LPS) co-receptor CD14 in stools collected from U.S. travelers to Mexico with and without travelers' diarrhea (TD)

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Sponsored by: Pablo C. Okhuysen, M.D.
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Supported by: The University of Texas at Houston Medical School - Summer Research Program

Key Words: CD14, travelers' diarrhea, LPS, bacterial enteropathogens

Forty to 60% of US travelers visiting Mexico are at risk for travelers' diarrhea (TD). Bacterial enteropathogens can be identified in 50-80% of cases and in a subset of travelers cause inflammatory diarrhea. CD14 is a glycosylphosphatidylinositol-linked (GPI) protein that is found in membrane-associated or soluble forms. CD14 is present on monocytes, macrophages, and in certain epithelial cells. CD14 is involved in innate immunity and interacts with LPS from Gram-negative bacteria resulting in the secretion of pro-inflammatory cytokines. We hypothesized that in subjects with bacterial TD, fecal CD14 would increase in response to infection and correlate with inflammation. Stool samples from subjects with TD (n=203) and from healthy subjects without TD (n=58) were studied for the presence of fecal CD14 by ELISA. CD14 was measurable in equal proportions ($p = NS$) in subjects with TD (50/203 or 25%) and in healthy controls (14/58 or 24%); In a subset analysis done on subjects in whom bacterial pathogens were identified, CD14 was more likely to be measurable in asymptomatic infection (23/33 or 70%) than in symptomatic infection (34 /121 or 28%; $P < 0.001$). Although a dilution effect may account for some of the differences observed, these data suggest that intestinal CD14 may play a role in the innate immune response to enteropathogens. Additional studies are needed to elucidate the role of intestinal CD14 in health and during bacterial diarrhea.

ABSTRACT

Clinical Features of Irritable Bowel Syndrome (IBS) A Patient Study at Kelsey Seybold Clinic (KSC)

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Sponsored by: Herbert L. DuPont, MD, Department of Infectious Disease and Internal Medicine

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

Key Words: IBS, Post-Infectious IBS, Diarrhea

The purpose was to study the clinical characteristics of an IBS patient population and to identify clinical features of post-infectious IBS (PI-IBS). A questionnaire was administered to 184 subjects at KSC with a diagnosis of "IBS". The Rome II criteria were employed to determine presence of IBS (AGA). PI-IBS was defined as IBS beginning with a bout of acute diarrhea or gastroenteritis as described by Dunlop et al. in 2003. Eighteen subjects failed to answer questions to allow a determination of IBS. Of the remaining 166, 137 (82.5%) met the criteria for IBS. The mean and median duration of IBS symptoms were 11.7 years and 8.5 years, respectively. Fifty-six of 176 (31.8%), answering this question, had a family member with IBS. Forty-two of 164 (25.6%) providing data met the criteria for PI-IBS. For surveyed IBS subjects after removal of those with PI-IBS, 30 of 126 (23.8%) indicated that their GI symptoms were worsened by a bout of diarrhea with 7 (23.3%) of these reporting that their GI symptoms being permanently worsened by the acute diarrhea bout. In these 30 subjects having their illness worsened by a bout of diarrhea, 21 (70%) experienced the diarrhea during travel. IBS is a common medical problem with a bout of diarrhea commonly preceding their chronic gastrointestinal disease and with previous travel commonly implicated in the antecedent diarrhea. PI-IBS and IBS beginning with or worsening by a bout of diarrhea during international travel is potentially preventable with antibiotic prophylaxis or enteric vaccines.

ABSTRACT

Title: Class-I Human Leukocyte Antigen and Systemic Sclerosis

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Sponsored by: Pravitt Gourh, MD

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

Key Words: Systemic sclerosis, Class-I HLA genes, autoimmunity

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterized by hardening of the skin along with autoantibody production and multiple organ involvement. Class-II Human Leukocyte Antigen (HLA) genes have been associated with SSc and its autoantibody and clinical subsets. Class-I HLA polymorphisms have been shown to be associated with type-1 Diabetes, Ankylosing Spondylitis, and Multiple Sclerosis. Previously, smaller studies in SSc have shown a possible correlation with Class-I HLA and SSc. HLA Class-I genes are located on Chromosome 6p21.3 and are responsible for presenting endogenous peptides to immune cells. This study's goal was to investigate the possible association between Class-I HLA genes and SSc.

SSc patients (498) were selected based on ACR criteria or at least 3 out of 5 CREST symptoms along with 500 healthy controls. PCR was performed using the DNA samples extracted from peripheral blood and was confirmed by agarose gel electrophoresis. HLA class-I genotyping was performed by sequence specific oligonucleotide probe hybridization as per manufacturers protocol (Invitrogen). These data will be analyzed using chi-square, Fisher's exact, logistic regression, and linkage disequilibrium tests.

Our patient cohort consisted of 89.8% female and 10.2% male SSc patients. The frequencies of the three major autoantibodies in our cohort were 29.5% for anticentromere, 18.1% for anti-topoisomerase-I, and 18.1% for anti-RNA Polymerase-III antibodies. Limited skin involvement was present in 66.5% and diffuse skin involvement was present in 33.5% of SSc patients. Currently, we are analyzing the class-I HLA genotyping data for association with SSc and its autoantibody and clinical subsets.

ABSTRACT

A Randomized Clinical Comparison of the Intersurgical I-Gel and LMA Unique in Non-Obese Adult Patients During General Surgery

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

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

Key Words: I-gel, Laryngeal Mask Airway (LMA), airway

Supralaryngeal airway devices have become popular over the past decade due to their ability to maintain an adequate airway without passing through the vocal cords, eliminating potential trauma. The purpose of our study was to compare the effectiveness of the Intersurgical I-gel with the current standard of supralaryngeal airway device, the Laryngeal Mask Airway Unique (LMA-U). Ease of insertion, airway position, airway seal, and patient vitals were recorded for 50 randomized, adult, non-obese patients undergoing general anesthesia for elective surgery. Patients with a known difficult airway or facial deformities were excluded from the study. Postoperative sore throat, hoarseness, and difficulty swallowing were also recorded.

Upon analysis of the data, it was determined there were no statistically significant differences between the I-gel and the LMA-U. The I-gel had 3 instances of failure (12%), in which an LMA-U was substituted due to low leak pressures. These patients were close to the weight suggestions for the I-gel device size. This research suggests modifications should be made to the weight suggestions. The I-gel was similar in use and effectiveness as the LMA-U. Further studies are indicated.

ABSTRACT

Identification of Virulence Determinants Required for *Borrelia burgdorferi* During Mouse Infection by Signature-tagged Mutagenesis

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

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

Key Words: *Borrelia burgdorferi*, signature-tagged mutagenesis

Lyme borreliosis is the most common vector-borne disease in North America and Eurasia. It is caused by *B. burgdorferi* and transmitted by tick *Ixodes scapularis*. Signature-tagged mutagenesis (STM) is a powerful negative selection method that has been widely used to identify bacterial virulence factors required for the successful adhesion, colonization, and dissemination in the host. A vast amount of information regarding virulence determinants has been derived from at least 31 bacterial species by using this technique.

Dr. Norris' lab has developed a signature tagged mutagenesis system for the isolation of borrelial virulence genes by adding 12 unique DNA sequence tags to the pMarGent derivative, pMarGentKan. In this manner, each mouse can be co-infected with 12 signature-tagged clones and examined for infection by assaying multiple organ sites for survival, dissemination, and outgrowth of each of the clones. Signature-tagged versions of the suicide *Himar1* transposon vector pMarGentKan were constructed by inserting STM tags into a region between the ColE1 origin and Inverted Repeat 2. The transformable, infectious *B. burgdorferi* strain 5A18NP1 was transformed using pMarGentKan with 11 STM tags.

We performed the STM experiments using C3H/HeN mice infected with 4 sets of pooled mutants. *Borrelia* mutants from *in vitro* and *in vivo* pools were identified by using PCR. Several potential virulence determinants are included in these groups. Four pools of 11 randomly selected STM mutants were inoculated subcutaneously into 3 C3H/HeN mice each. The mouse infectivity studies conducted indicate that some of selected STM mutants might be previously unidentified virulence determinants.

ABSTRACT

Families with Lujan-Fryns Syndrome present no mutations in MED12 and UPF3B

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Sponsored by: Dianna M. Milewicz, M.D, PhD, Department of Medical Genetics

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

Key Words: Lujan-Fryns, x-linked mental Retardation, MED12, UPF3B

Lujan-Fryns Syndrome (LFS), an X--linked mental retardation syndrome with Marfanoid habitus, is a rare genetic disease known to cause mild to moderate mental retardation and skeletal dysmorphisms. Affected individuals are predominantly males, proving the recessive nature of this disease. Mutations in two genes found in the X chromosome, MED12 and UPF3B, were previously identified as causes of LFS. The MED12 mutation was a missense mutation in exon 22, while twomutations were identified in UPF3B in exons 9 and 10. Three new families diagnosed with LFS are introduced in this study. DNA was collected from the family members. DNA from three affected males (one from each family) was sequenced for MED12 and UPF3B mutations using intron-based, exon-specific primers in order to look for novel mutations in these genes leading to LFS. After analyzing the results, only one unreported deletion in the 3' UTR of exon 32 was identified. When compared to controls of the same ethnicity, we found that this deletion was also present in control DNA, discarding the alteration as a cause of LFS. Our results and the known genetic heterogeneity of the disease suggest the possibility of alterations in a third gene as the cause of LFS in these three families. Future gene mapping of these families should lead to the identification of the unknown gene/s.

ABSTRACT

Identification of *Bacillus anthracis* trans-acting regulators of *atxA* transcription using transposon mutagenesis

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Key Words: *Bacillus anthracis*, *atxA*, screen

Virulence gene expression by *Bacillus anthracis*, the causative agent of anthrax disease, is dependent upon *atxA*, encoding the Anthrax Toxin Activator. *AtxA* is required for transcription of the structural genes for the anthrax exotoxins, lethal toxin and edema toxin, as well as transcription of the biosynthetic operon for the antiphagocytic poly-D-glutamic acid capsule. The regulation of *atxA* is complex and not completely understood. Transcription of *atxA* is controlled by a feedback mechanism involving the transition state regulator *AbrB*, the alternative sigma factor σ^H , and the master response regulator *Spo0A*. My goal was to use transposon-mediated mutagenesis of a *B. anthracis* reporter strain to identify additional factor(s) involved in the complex regulatory network that controls *atxA* transcription. To produce this library, a construct containing the *atxA* promoter (*PatxA*) fused to the β -galactosidase gene *lacZ* was created for integration into the native *atxA* chromosomal locus. Once the reporter construct is confirmed, it will be used to integrate the *Patxa-lacZ* fusion into the native *atxA* locus. The transposon vector will be introduced into the *B. anthracis* *PatxA-lacZ* reporter strain using electroporation. Approximately 5×10^4 *B. anthracis* transposon mutants will need to be screened to achieve complete coverage of the genome. Insertion sites of transposons in mutants of interest will be determined using inverse PCR. This experimental approach will provide researchers with a better understanding of the overall mechanism of virulence gene regulation in *B. anthracis*.

ABSTRACT

Is the glutamate in pre-frontal cortex involved in acute and chronic response to psychostimulant treatment?

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

Key Words: Methylphenidate (MPD), Attention Deficit Hyperactivity Disorder (ADHD), Prefrontal cortex (PFC), ibotenic acid lesions, behavioral sensitization.

Approximately 5 – 13% children in the United States have Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate (MPD) is a psychostimulant used to treat ADHD. Repeated injections of MPD cause sensitization, i.e. augmentation of behavioral response following repetitive administration of the drug. Exact mechanisms underlying sensitization are unclear. However, neural mechanisms underlying sensitization are known to be similar to those underlying compulsive drug seeking behavior. Research regarding mechanisms of sensitization could help us understand drug-induced plasticity and prevent the abuse liability of psychostimulants.

It was recently reported that pre-frontal cortex (PFC) is involved in the development of sensitization using non-specific electrolytic PFC lesions. The aim of this study was to study the role of the PFC glutamate system in the effects of acute and chronic MPD administration by pacing specific glutamate neurotoxin (ibotenic acid) to produce lesions at the PFC. Male Sprague-Dawley rats were divided into three groups: (1) an intact control group (n = 8), (2) a sham group (n = 5), and (3) a lesion group (n = 10). The open field assay was used to record the locomotor activity after saline injections before and after surgery for baseline, followed by recordings on the first and last day of the six day regimen of 2.5 mg/Kg MPD injections, recordings on the first and last day of four days of washout, and recording post 2.5mg/Kg MPD rechallenge injection.

The data is under analysis.

ABSTRACT

IFN- γ Production as a Measure of Immune Response in Thermochemotherapy Cancer-Cured Rats

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Key Words: interferon-gamma, ELISpot, oxaliplatin, thermochemotherapy

Background: Immunologically normal female Fischer rats previously orthotopically implanted with the syngeneic MTLn3 mammary adenocarcinoma were used as the tumor model. Ten days after tumor inoculation, tumor bearing rats were treated with an optimally scheduled and dosed regimen of oxaliplatin and fever-range whole body thermal therapy (FR-WB-TT). Fifty percent of treated rats had all growing primary tumors and metastases completely respond, and the syngeneic tumor could not be reinduced in these rats. Hence they were considered cured. The cured rats were used in this experiment to study the possible immune mechanism associated with complete tumor response and cure. Purpose: The purpose of this study was to investigate a potential mechanism of thermochemotherapy-induced immune response in cured rats re-challenged with MTLn3 tumor cells by determining the frequency of peripheral blood mononuclear cells (PBMCs) releasing interferon-gamma (IFN- γ). IFN- γ is produced by memory CD8+ T cells. Materials and Methods: One cured rat received re-implantation of MTLn3 cells 2 days before blood draw and one cured rat received re-implantation 5 days before blood draw. PBMCs were harvested from the blood. The frequency of MTLn3 stimulated PBMCs releasing IFN- γ was determined by ELISpot assay. Positive controls were interferon-gamma, and cells stimulated by Concanavalin A (ConA). Negative controls were cells stimulated by glioblastoma, tumor cells only, or unstimulated PBMCs. Conclusion: The frequency of cells releasing IFN- γ was significantly greater in cured rats restimulated with MTLn3 compared to rats restimulated with glioblastoma cells, another syngeneic tumor. This suggests that an adaptive CD8+ lymphocyte antigen-specific immune response was induced by the appropriately timed and dosed thermochemotherapy, thus leading to the cure.

ABSTRACT

Dynamics of cardiolipin domains in the *Escherichia coli* membrane

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

Key Words: bacteria, membrane domains, cardiolipin

Phospholipid membrane domains have been observed at cell poles and division sites in bacteria. To provide the basis for a mathematical model of the formation of cardiolipin (CL, one of the major anionic phospholipids) domains at a certain stage of the cell cycle, we stained wild-type *Escherichia coli* with the CL-specific fluorescent dye 10-*N*-nonyl-acridine orange (NAO). We viewed the cells using a Delta Vision wide-field optical sectioning microscope equipped with a FITC filter set. After deconvoluting the images, we found that CL domains consistently form at the mid-cell area prior to constriction, the physical beginning of binary fission. Time-lapse fluorescence microscopy of the NAO-stained cells confirmed these results. Such findings are consistent with the proposed role for mid-cell CL domains in organizing cell division proteins into the divisome structure necessary for the division of a cell into equal halves. Fluorescence microscopy of NAO-stained cells was also performed on a phosphatidylethanolamine (PE)-lacking *E. coli* mutant (*pss93::kan*) bearing a plasmid-borne copy of the *Legionella pneumophila pcs* gene encoding phosphatidylcholine (PC) synthase. The replacement of PE by PC provided a new model for studies of CL domain formation. Preliminary results demonstrate partial suppression of the cell division inhibition phenotype of the *pssA* null mutant containing only anionic phospholipids by the foreign phospholipid PC. Experiments are currently underway to describe CL-domain localization in the PC-producing cells. Such attempts to understand the role of phospholipid domains in bacterial cell division are important to the field of pharmacology for the development of antimicrobial drugs.

ABSTRACT

Screening for Adenylyl cyclase N-terminus interaction with G proteins and AKAPs

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Key Words: Adenylyl cyclase, N-terminus, G proteins, AKAPs

Adenylyl cyclase (AC) catalyzes conversion of ATP to cyclic AMP, an important second messenger in physiological functions. The alpha subunit of the heterotrimeric G protein G_s stimulates AC to produce cyclic AMP. AC is membrane bound, and is composed of a cytosolic N-terminus, a transmembrane domain [M1], a cytoplasmic domain [C1], and a repeat of these domains [M2] and [C2]. The C1 and C2 domains form the catalytic core and the N-terminus (NT) is also important for regulator interactions. There are nine isoforms of transmembrane ACs and these are regulated in isoform specific manner. ACs are regulated by G-proteins, anchoring proteins (AKAPs), forskolin, and protein kinases. All isoforms are stimulated by GTP bound G_s . $G_{\beta\gamma}$ inhibits AC 1, 3 and 8; it stimulates AC 2, 4, 5, 6 and 7 in presence of G_s . Studies show that $G_{\beta\gamma}$ binds to C domains in AC2, but also NT-AC5 and 6. Unpublished results from the lab show AKAP79 binds to the NT-AC5 while AKAP Yotiao binds to NT-AC2. The goal of the project was to determine whether N-terminus of other ACs, namely AC3, 6 and 9 interact with G-protein subunits, AKAP79, Yotiao or mAKAP.

GST-tagged NT-AC6 and 9 were purified using glutathione agarose resin. In GST pull down assays using NT-AC 2, 3, 5, 6, and 9, it was found that GDP. G_{α} and $G_{\beta\gamma}$ bind to NT-AC 6 and 9. No binding was observed with GST alone or with GST-NT AC3. AKAP79 binds NT-AC5, 6 and 9. Additional studies with Yotiao and mAKAP are in progress.

ABSTRACT

Protection of Intestinal Epithelial Cells from Hypoxia-induced Disruption of Barrier Function by Probiotic *Lactobacillus rhamnosus* GG

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Key Words: Hypoxia, tight junction, probiotics, *Lactobacillus rhamnosus*, TEER

Hypoxia has been implicated in the breakdown of the intestinal epithelial barrier. Neonates with immature immune systems may be at greater risk for developing sepsis after such conditions as necrotizing enterocolitis. *Lactobacillus rhamnosus* GG (LGG), a natural occurring bacterium originally isolated from the healthy human intestine, is one of the best-studied probiotics in clinical trials for treating and preventing several intestinal disorders, including diarrhea and infections. The effect of LGG on tight junctions is unknown. We determined the possible detrimental effect of hypoxia on the barrier function and evaluated the effect of LGG on disruption of tight junctions in porcine intestinal epithelial cell line, IPEC-J2. The IPEC-J2 cells formed polarized monolayers in collagen-coated transwell inserts after 15-days of culturing. Monolayers were treated with LGG at 9×10^8 CFU/mL for 5 h before exposure to either hypoxia (5 % carbon dioxide and 95 % nitrogen) or normoxia. Barrier function was evaluated by measurement of transepithelial electrical resistance (TEER) at the end of every hour of hypoxia or normoxia. The tight junction protein occludin was detected by immunofluorescent staining. The TEER of IPEC-J2 cells displayed a steady increase from 1 to 5 h of hypoxia and dramatically decreased after 6 h concomitant with monolayer disruption. However, the TEER of cells pretreated with LGG didn't change throughout the process. The distribution of occludin at cell-cell junctions was disrupted by hypoxia, while it remained intact after pretreatment with LGG. In conclusion, hypoxia-induced disruption of the tight junction can be prevented by LGG.

