2007

Summer Research Program

Student Abstracts

The University of Texas
Health Science Center at Houston
Contents

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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 analyses, 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 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.

This the third year of a new program which was initiated for international medical students from schools with whom we have cooperative agreements. These international medical students perform research and participate in all of the Program’s supplemental activities. Abstracts submitted by the international medical students are in this publication (see the International Medical Students section.)

UTHMS student research training is supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and 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

Student Abstracts, Volume XXII, Summer 2007
Acknowledgements

This publication marks the completion of the twenty-second 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 former Interim Dean Jerry Wolinsky, M.D., and to Patricia M. Butler, M.D., Associate Dean, Office of Educational Programs, who continue to insure the yearly success of the Summer Research Program. Our new Dean, Dr. Guiseppe Colasurdo, has indicated his strong support for our program, and for the medical students who wish to perform research.

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 T35 DK007676).

Dr. Hui-Ming Chang, Vice President for International Programs and Special Advisor to the President, 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 expand into 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 on an abstract and public presentation of results. Our sincere appreciation to all faculty mentors.
Lab Research Ownership

Publication and/or Disclosure

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

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

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

“Because your research was generated from ideas and funds that originated with your faculty mentor and The University of Texas Medical School at Houston, ownership of any data generated by you during the Summer Research Program belongs to The University of Texas Medical School at Houston or the Principle Investigator (PI).”
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### 2007 International Medical Students

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- These students were sponsored by the Graduate School of Biomedical Sciences.
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Medical Students
Functional Magnetic Resonance Imaging Investigation of Amphetamine Influence on Impulsive Behavior

KELLEY D. BABCOCK  The University of Texas at Houston Medical School  Class of 2010

Sponsored by:  Joel L. Steinberg, MD, Department of Psychiatry and Behavioral Sciences
               F. Gerard Moeller, MD, Department of Psychiatry and Behavioral Sciences

Supported by:  The Bernard Saltzberg Summer Research Fellowship

Key Words:  dextroamphetamine, fMRI, event-related, Go-NoGo, prefrontal cortex

Background: This study measured neural correlates of impulsive behavior in healthy subjects after administration of placebo and amphetamine using functional magnetic resonance imaging (fMRI). Substance abuse, particularly stimulant use, is associated with impulsive behavior (Moeller et al., 2001), and so investigating the neural basis behind this could provide new insights into amphetamine abuse prevention and treatment.

Methods: Screened subjects were studied only if negative for personality/mental disorders and drug use. Each subject was scanned after administration of placebo and dextroamphetamine on two separate days. They then underwent rapid presentation, stochastic, parametric event-related design fMRI while performing a Go-NoGo task. The test design had two “No-Go” stimuli: easy and hard. Image processing provided stereotaxic coordinates (Talairach and Tournoux, 1988) where Blood Oxygen Level Dependent (BOLD) neuronal activation occurred. Images were spatially smoothed with a Gaussian filter and analyzed with SPM2.

Results: This study found that after amphetamine there was less activation in the prefrontal cortex compared with placebo.

Conclusion: As the prefrontal cortex is associated with central executive function, it can be suggested that the amphetamine trials required less central executive function to correctly withhold from a No-Go stimulus, and thus became more automatic. However, because of the small number of subjects and fixed effects analysis, these results cannot be generalized to the population from which these subjects were drawn. Thus, this analysis should be regarded as a case study.
ABSTRACT

The Role of C5a Dependent Metalloproteinase Regulation in Kidney Disease

STEPHANIE T. BATES  The University of Texas at Houston Medical School  Class of 2010

Sponsored by:  Michael C. Braun, MD, Institute of Molecular Medicine

Supported by:  Michael C. Braun, MD, Institute of Molecular Medicine

Key Words:  C5a receptor, glomerulonephritis, Factor H, MMP, GBM

Deficiency in the regulatory complement protein Factor H (FH) is associated with Membranoproliferative Glomerulonephritis in humans, and homologous renal injury in mice. Previous work in our lab has shown that FH deficient mice lacking the complement C5a receptor have increased glomerular basement membrane deposits and altered renal expression of matrix metalloproteinases (MMP); enzymes that modulate extracellular matrix turnover. This study sought to define the specific effects of C5a receptor-dependent MMP production in vitro.

Primary mesangial cells were isolated from C57BL/6 (WT), FH, and Factor H/C5a receptor deficient (FHC5aR) mice and cultured with WT, FH and FHC5aR mouse sera. After 96 hours in culture, the cells were harvested and MMP 2, 7, 9 and 12 mRNA expression analyzed using quantitative RT-PCR. In comparison to controls, FHC5aR cells exhibited a 30 and 35 fold decrease in MMP 9 and 12, respectively. Cell supernatants were collected at 24, 48, 72, and 96 hours post-stimulation and changes in MMP production were confirmed by Western blot. Zymography using both gelatin and elastin as substrates demonstrated substantially decreased MMP activity in supernatants from FHC5aR cells compared to controls.

These data indicate that the C5a receptor plays a major role in regulating selective MMP expression in murine mesangial cells. FHC5aR cells had the lowest levels of MMP 9 and 12 production and activity, which supports the in vivo finding that FHC5aR deficient mice manifest the most severe glomerular lesions. This study provides novel insights into complement activation and localized regulation of MMPs in renal disease.
ABSTRACT

Serotonin (5-HT)-Induced Long-Term Changes in Excitability (LTE) in Cultured Sensory Neurons (SNs)

PETER A. BOURELL      The University of Texas at Houston Medical School      Class of 2010
Sponsored by:      Dr. John Byrne, PhD, Department of Neurobiology and Anatomy
Supported by:      Dr. John Byrne, PhD, Department of Neurobiology and Anatomy
Key Words:      LTE, SN, 5-HT, culture, Aplysia

Learning is associated with changes in the intrinsic excitability of individual neurons. Although it is generally agreed that long-term excitability (LTE), the responsiveness of a neuron to an applied stimulus, is a ubiquitous feature of the storage of memory in individual neurons, there is controversy as to whether LTE is induced and expressed in an isolated cell or whether it requires a neuron be part of a functional neuronal circuit. For example, Dale et al (1987) found that the neuromodulator serotonin (5-HT) induced LTE in isolated sensory neurons (SNs) from Aplysia 1 day following treatment, whereas Cai et al (2005) found that retrograde factors from a postsynaptic neuron were required for LTE in SNs.

The purpose of my research was to explore an alternative hypothesis. Specifically, that the differences in the literature could be due simply to the nature of the culture medium and the age of the cells. Indeed, LTE was observed when 2-day old cultures were treated with 5-HT and tested in a hemolymph/L15 medium and maintained throughout in artificial saltwater (ASW)/L15 medium. These findings supported the original results of Dale et al (1987). However, LTE was no longer observed when 2-3 day old neurons were tested in an ASW/L15 medium and maintained in a hemolymph/L15 medium. In conclusion, the preliminary results indicate that LTE is dependent on the cell medium and the age of the cells, and that the presence of a postsynaptic cell is not necessary for its induction and expression.
ABSTRACT

Silica and Carbon Nanotubes are Potentially Harmful to Human Cells

CRYSTAL M. BOWDEN       The University of Texas at Houston Medical School       Class of 2010

Sponsored by: Xiaodong Zhou, M.D.; Department of Internal Medicine and Rheumatology
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15

Key Words: Silica, Carbon Nanotubes, Fibroblasts, Macrophages, T cells

Objective: Silica- and carbon nano-particles are widely existent in our living environment. Some reports have indicated they might be hazardous to human health. Our purpose was to determine potential pathogenic effects of these two particles to cultured human cells.

Methods: Macrophages were stimulated with either silica, carbon nanotubes or titanium (10 μg/ml) for 24 hours. PBS was used for negative control. Cultured normal human T cells were mixed with stimulated macrophages for 10 minutes and then added to cultured normal human skin fibroblasts. Cells and culture media were extracted at 1 and 24 hours. ELISA arrays were used to examine cytokine levels in cultured medium. Gene microarrays (Illumina ref8) were used for profiling transcript levels of fibroblasts responding to stimulated macrophages/T cells.

Results: Both silica- and nanotube-stimulated macrophages induced a high level (≥3 fold) of IL1α and β in culture medium of fibroblasts with macrophages and T cells after 1 hour. Nanotube-stimulated macrophages also increased levels of IL8 (≥6-fold) and IL13 (≥2-fold) in culture medium at 1 hour. Gene expression of fibroblasts cultured with either silica- or nanotube-stimulated macrophages/T cells for 24 hours showed an up-regulation of transcript levels of COL1A and IL1β (p<0.001). In addition, inflammation related and collagen genes such as TGFB3 and COL10A1 were up-regulated in fibroblasts cultured with nanotube-stimulated macrophages/T cells. Microscopic examination of live-cultured cells showed centralization of macrophages and T cells around the carbon nanotubes with deformed fibroblasts. In contrast, the fibroblasts in the presence of titanium-stimulated macrophages/T cells did not show similar changes as above.

Conclusion: Up-take of silica and carbon nanotubes by macrophages induced activation of T cells and fibroblasts toward inflammatory and fibrotic pathways. These observations strongly suggest the potential pathogenic effect of silica and carbon nanotubes to human cells.
ABSTRACT

The Role of Ventral Tegmental area of the Brain Stem on the Immediate and Long (Circadian Activity) Effects of Methylphenidate (Ritalin)

ALONSO CARRASCO     The University of Texas at Houston Medical School     Class of 2010

Sponsored by:     Nachum Dafny, Ph.D., Department of Neurobiology and Anatomy
                 Allan C. Swann, M.D., Department of Psychiatry

Supported by:     Pat Rutherford Chair in Psychiatry
Key Words:     Methylphenidate, Ventral tegmental area, Ritalin

Methylphenidate (MPD), commonly known as Ritalin, is the drug most often used to treat attention deficit/hyperactivity disorder (ADHD). MPD is a psychostimulant that binds to the dopamine (DA) transporter and prevents the re-uptake of DA. Studies have shown that repeated administration of psychostimulants such as cocaine and amphetamine results in tolerance, withdrawal, or behavioral sensitization, which are markers for its dependant properties. Initiation of behavioral sensitization has been link to occur in the ventral tegmental area (VTA). Previous studies with MPD found that a dose of 2.5 mg/kg of MPD results in behavioral sensitization in rats. The objective of the present study is to investigated the role of VTA in MPD elicit sensitization using adult male Sprague-Dawley (SD) rats with and without bilateral specific chemical lesion of DA neurons in the VTA using the neurotoxin 6-hydroxydopamine. Animals were divided into 3 groups, control, sham surgery, and lesion group respectively. An open field assay was use to record five locomotor indices 24 hours/day for 11 days. The data analysis was divided into 4 phases, acute, inductive, withdrawal, and expression. The results obtained show that the control and sham groups express sensitization and significant alteration of their circadian activity pattern while the lesion group failed to express sensitization but did exhibit change in the circadian activity pattern to chronic MPD treatment. This study shows that VTA DA is essential for the expression of sensitization, but not for the change in circadian activity pattern.
ABSTRACT

Prevalence of *bacteroides fragilis* and *arcobacter* in Travelers’ Diarrhea in Guadalajara, Mexico

*JACLYN CHEN*  
*The University of Texas at Houston Medical School*  
*Class of 2007*

Sponsored by: Herbert L. DuPont, MD, Department of Internal Medicine, Infectious Diseases  
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15  
Key Words: Bacteroides fragilis, Arcobacter, Travelers’ diarrhea

Despite advances in characterizing the epidemiology and etiology of acute diarrhea occurring in international travelers, the cause remains uncertain in nearly half of cases. Identifying new enteropathogens is important in developing principles for disease treatment and prevention. In several areas of the world strains of *Bacteroides fragilis* (BF), positive for production of an enterotoxin known as enterotoxigenic BF (ETBF), have been associated with pediatric diarrhea. The present study sought to detect ETBF in travelers’ diarrhea (TD). Forty-three U.S. adult (≥ 18 years of age) students with acute diarrhea (passage of ≥ 3 unformed stools plus one or more signs or symptoms of enteric infection including nausea, vomiting, abdominal cramps or pain, fecal urgency or tenesmus of no more than 72 hours duration) acquired in Guadalajara, Mexico during the summer of 2007 were enrolled in the study. After signing a consent form, the subjects provided an illness stool which was collected in a wide-mouthed plastic cup and transported to a school clinic maintained by the University of Texas – Houston (UT-H). Fecal samples were transported twice a day to the UT-H laboratory in Guadalajara. For BF identification, the sample was plated onto *Bacteroides* bile esculin (BBE) agar and incubated in anaerobic jar at 37°C for 48 hours at which time the organism was identified as small black colonies. In addition to microbiologic identification methods for BF, DNA and RNA were extracted from each fecal sample by conventional methods and stored at -20°C before transporting to Houston for later PCR studies. BF was identified in 18/43 (42%) of subjects with diarrhea. The 18 BF isolates were mixed with 1mL of PBS in a 1.5mL tube, pelleted and lysed with resultant DNA extracted for transporting to Houston. At the UT-H laboratories in Houston, the DNA was then eluted with 50 µL of DNA Hydration Solution/TE buffer with resultant detection of ETBF by PCR using a BF1 and BF2 primer set to amplify the 294 bp enterotoxin gene product. The reaction mixture contains deoxynucleoside triphosphates (200µM each), 25 pmol of each primer, Taq DNA polymerase (1U), and 10µL of DNA template in a final volume of 100µL of PCR buffer containing 1.5mM MgCl₂. Samples were subjected to 35 amplification cycles carried out in a DNA thermal cycler. Each cycle consists of 1 min. of denaturation at 94°C, 1 min. of annealing at 52°C, and 1 min. of extension at 72°C. The last cycle is followed by 5 mins. of extension at 72°C. Amplified DNA (10µL) is subjected to electrophoresis in a 1% agarose gel containing 0.5 µg of ethidium bromide per ml at 90mV for 70 minutes. The DNA bands were visualized and photographed under UV light. ETBF was identified by PCR in 10 of 43 (23.3%) diarrheal stools. ETBF was identified by PCR in 6/18 (33.3%) BF colony cultures. The following conclusions are drawn in the study: 1) direct fecal PCR represents a more sensitive method of detection than microbiologic culture of BF for the identification of ETBF; 2) ETBF appears to represent an important newly identified enteropathogen in TD. Future studies are being designed to confirm the importance of ETBF in TD and to demonstrate a host immune response to the enteropathogen to help establish an etiologic role.
ABSTRACT

Explanations for Unsuccessful Weight Loss Among Seekers of Bariatric Surgery

JOSEPH H. CHILDS  The University of Texas at Houston Medical School  Class of 2010

Sponsored by:  Kevin O. Hwang, MD, Department of Internal Medicine
Supported by:  National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words:  Obesity, Bariatric surgery, Weight loss

We analyzed subjective explanations for unsuccessful weight loss among individuals seeking bariatric surgery at UT. Self-reported explanations for unsuccessful weight loss were indicated by response to the open-ended question, “How do you personally account for why you have not been able to lose weight?” The coding scheme was generated by identifying categories from previous studies, clinical experience, and iterative review of random samples. Chi Square was used to test associations with predictor variables of age, gender, ethnicity, and initial body mass index (BMI). From 1,927 individuals seeking bariatric surgery; 47% (909) responded to the question (78.2% female and average BMI 47.3). The most common categories were non-specific explanations related to diet (25.3%), physical activity (21.0%), or motivation (19.7%), followed by diet-related motivation (12.7%) and medical conditions or medications affecting physical activity (12.7%). Categories related to time, financial cost, social support, physical environment, and knowledge occurred less than 4% each. Men were more likely than women to cite a medical condition or medication affecting physical activity (19.2% vs 10.8%, \( P=0.002 \), OR=1.96, 95% CI=1.28-2.99) but less likely to cite diet-related motivation (7.1% vs 14.2%, \( P=0.008 \), OR=0.46, 95% CI=0.26-0.82). Age, BMI, and ethnicity were not consistently related to explanations for unsuccessful weight loss. In conclusion, bariatric surgery seekers cite motivation related factors to explain unsuccessful weight loss more often than time, financial cost, social support, physical environment, and knowledge. Gender differences also exist. These findings may aid in designing weight loss interventions.
Molecular Mechanism of Unloaded-Mediated Cardioprotection in Ischemia/Reperfusion Injury: Possible Role of endothelin-1 down-regulation?

JOHN L. COLQUITT  The University of Texas at Houston Medical School  Class of 2010

Sponsored by: Richard W. Smalling, M.D., Department of Internal Medicine
Supported by: Richard W. Smalling, M.D., Department of Internal Medicine
Key Words: Reperfusion injury, endothelin, unloading

Ischemia/reperfusion injury is a curious phenomenon observed during treatment of myocardial infarction. While recognized for its capacity to save lives, reperfusion can also exacerbate myocyte damage and hasten the death of injured myocardial cells. Endothelin-1 (ET-1) has been shown to play a role in reperfusion injury. Released during reperfusion, ET-1 may contribute to left ventricular dysfunction by increasing apoptosis within the ischemic region. Previous research has shown that decreasing left ventricular pressure work during ischemia/reperfusion salvages myocardial tissue and decreases infarct size. Our objective was to elucidate the cardioprotective mechanism(s) of mechanical unloading in a rabbit ischemia/reperfusion model. We speculated that the reduction of ventricular mechanical stress achieved by unloading mediates the down-regulation of ET-1 release, increasing the levels of anti-apoptotic proteins, which in turn inhibit the loss of myocytes. Anesthetized New Zealand white rabbits were subjected to one hour of left circumflex coronary artery occlusion followed by three hours of reperfusion. Unloading- initiated fifteen minutes prior to reperfusion and then maintained throughout reperfusion- was accomplished with a peristaltic pump by means of a ventricular-femoral artery bypass. To assess ET-1 levels, radio-immuno assays were performed on plasma samples. For tissue protein analysis, western blotting was employed. Preliminary results show decreased ET-1 release within the unloaded group after 2 hours reperfusion [21.37 ± 2.83 pg/mL vs. 54.34 ± 11.34 pg/mL, P=0.03], while anti-apoptotic Bcl-2 protein levels show an increase in the unloaded group. Left ventricular unloading promotes cardioprotection during ischemia/reperfusion by decreasing the release of ET-1; consequently, less apoptosis occurs within the ischemic region.
Signal Among Noise: the Effect of Noise Adaptation on Discrimination Ability

JOSHUA C. COURSEY  The University of Texas at Houston Medical School  Class of 2010

Sponsored By: Valentin Dragoi, PhD, Department of Neurobiology and Anatomy
Supported By: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: Psychophysics, visual noise, discrimination, adaptation

One remarkable feature of the visual system is its astonishing capacity to maximize the signal from incoming inputs gathered by retinal circuits, and then convey the signal to visual cortex. Although the ability of cortical circuits to extract information from noise is just beginning to be understood, the exact impact of visual noise on behavioral performance is unclear. The purpose of my experiments was to investigate the visual system's ability to acquire information about stimulus orientation when noisy stimuli are rapidly presented in time. Three human subjects were asked to fixate at the center of a computer screen while adapting stimuli were presented binocularly. The adapting stimuli consisted of one of three oriented gratings (45°, 115°, or 135°), each presented at one of four noise levels: 0%, 70%, 90%, or 100%. Immediately following the adaptor, subjects performed a parallel discrimination task that measured their ability to judge small differences in stimulus orientation. The data obtained from these experiments will be used to determine subjects' psychophysical thresholds and construct psychophysical orientation tuning curves. We expect that adaptation to gratings of successively higher levels of visual noise will alter the subjects' orientation discrimination thresholds and produce shifts in tuning curves consistent with the orientation tilt aftereffect. These findings would support the hypothesis that high levels of noise in the adaptor do not completely abolish the ability of the visual cortex to accurately extract stimulus orientation.
Correction of Angular Deformity in Blount Disease: Staples vs. 8-plates

COURTNEY J. EL-ZOKM  The University of Texas at Houston Medical School  Class of 2009

Sponsored by: Allison C. Scott, MD, Department of Orthopaedic Surgery and Shriners Children’s Hospital
Supported by: Shriners Children’s Hospital
Key Words: Blount, staples, 8-plates, mechanical axis deviation

Blount disease in the pediatric population is being treated successfully with the use of staples and 8-plates. It is documented that both of these treatments correct angular deformity when applied at the appropriate time in skeletal growth. However, the comparison between the two treatments with respect to the amount of angular correction achieved hasn’t been studied. Therefore, we retrospectively compared study patients at Shriners Hospital for Children (SCH) and correlated treatment type to correction and time. Twenty-two patients diagnosed with infantile (10) or adolescent (12) Blount disease at SCH between 1/1/1990 and 1/1/2006 were studied. The patients had no prior surgical events or other diagnosis with secondary bowing. Surgical events, mean age: 40; 8.8 years. At time of surgery and follow-up the age, mechanical axis deviation (MAD), and anatomic Tibial-Femoral Angle (TFA) were measured. Follow-up defined as: staple/plate removed, medial side operated on, skeletal maturity, latest available radiograph, and epiphysiodesis. Results in Table:

<table>
<thead>
<tr>
<th>Amount of Correction</th>
<th>Staples</th>
<th>8-Plates</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAD (cm)</td>
<td>(-1.9±3.4)</td>
<td>(-1.6±2.2)</td>
<td>0.834</td>
</tr>
<tr>
<td>TFA (°)</td>
<td>(-5.6±11.3)</td>
<td>(-11.3±11.5)</td>
<td>0.188</td>
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</table>

<table>
<thead>
<tr>
<th>Amount of Correction per year</th>
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<table>
<thead>
<tr>
<th>Amount of Correction</th>
<th>Staples</th>
<th>8-Plates</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAD (cm)</td>
<td>(-1.1±2.5)</td>
<td>(-1.0±1.6)</td>
<td>0.882</td>
</tr>
<tr>
<td>TFA (°)</td>
<td>(-3.1±8.5)</td>
<td>(-7.4±8.8)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

| Infantile vs. Adolescent Blount Disease per year |

<table>
<thead>
<tr>
<th>Infantile</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>MAD (cm)</td>
<td>(-.6±2.8)</td>
<td>(-1.5±1.3)</td>
<td>0.427</td>
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<tr>
<td>TFA (°)</td>
<td>(-2.2±10.5)</td>
<td>(-10.3±7.4)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Adolescent</th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>MAD (cm)</td>
<td>(-1.1±2.4)</td>
<td>(-1.0±.9)</td>
<td>0.247</td>
</tr>
<tr>
<td>TFA (°)</td>
<td>(-2.7±6.4)</td>
<td>(-2.9±4.1)</td>
<td>0.258</td>
</tr>
</tbody>
</table>

When examining overall correction, there was little difference between staples and 8-plates on the MAD. However, there was a trend for 8-plates with 2 1/2 times the correction for the TFA per year.
Development of an \textit{In-vitro} Biofilm Model for Diabetic Foot Ulcer Infections

\textbf{SHAWN FUNK} \hspace{1cm} The University of Texas at Houston Medical School \hspace{1cm} Class of 2010

Sponsored by: Heidi B. Kaplan, PhD, Department of Microbiology and Molecular Genetics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: Biofilm, Quantitative Analysis, Confocal Microscopy

Diabetic foot complications such as ulceration, infection, and gangrene are the leading cause of hospitalization of the more than 20 million Americans with diabetes. The incidence of diabetic foot ulcer infections (DFUI) in these patients is 20-25\%, results in approximately 100,000 amputations per year, and costs billions of dollars. DFUIs result from persistent polymicrobial surface-associated infections of the soft tissue and bone, which are termed biofilms. We have developed a novel \textit{in vitro} DFUI model that replicates the unique growth characteristics of these biofilms and have created new analysis algorithms. For the model, hydroxyapatite (HA) or polymethylmethacrylate (PMMA) bone cement was formed into discs and used as growth substrate for \textit{Staphylococcus aureus}, which is the most common etiological agent of DFUIs. The discs were incubated statically at 37°C in a synthetic synovial fluid (SSF) or Dulbecco’s Modified Eagle’s Medium (DMEM) with low or high glucose that was changed daily. The biofilms were stained with the fluorescent BacLight LIVE/DEAD cell viability kit and imaged using a Zeiss 510 Meta Confocal microscope on days 3, 4, and 5. Quantification of the data (biovolume, substratum coverage, and thickness) was accomplished using new image analysis algorithms based on a previously published software package (PHLIP). The improved program was optimized for large data sets and the BacLight staining kit. The most effective DFUI biofilm conditions were determined to be HA discs with SSF. This model will be used in the future to evaluate the effectiveness of various antibiotics in inhibiting formation of polymicrobial DFUI biofilms.
ABSTRACT

Evaluation of Seroma Development following Abdominal Reconstruction of the Massive Weight Loss Patient

STEVEN L. GORDON    The University of Texas at Houston Medical School    Class of 2010

Sponsored by:    David J. Wainwright, MD, Department of Surgery – Division of Plastic and Reconstructive Surgery
Supported by:    Division of Plastic and Reconstructive Surgery, The University of Texas at Houston Medical School
Key Words:    Seroma, abdominoplasty, bariatric

As obesity reaches epidemic proportions globally, the need for bariatric surgery has increased significantly. Since these procedures frequently leave patients with excess skin that lead to additional problems, a subsequent reconstructive abdominoplasty is often a medical necessity. The most observed post-operative complication in this group is the development of a seroma, an accumulation of interstitial fluid between the abdominal wall muscular fascia and the subcutaneous tissue. The most noted factor in literature associated with seroma incidence is Body Mass Index (BMI) at time of surgery.

Purpose: The objective of this study was to investigate factors associated with increased fluid accumulation following abdominal reconstruction of the massive weight loss patient.

Methods: A retrospective chart review of 48 consecutive patients from January 2003 to June 2007 was performed. Factors to be evaluated were grouped into five categories: patient demographics, bariatric surgery history, pre-operative data, operative data, and post-operative data. Depending on the number of weeks before all drains were removed and all necessary aspirations were completed, patients were divided into three predetermined groups as follows: 1. Mild fluid accumulation (<2 weeks) 2. Moderate fluid accumulation (2-4 weeks) 3. Severe fluid accumulation (≥4 weeks). The epidemiological factors were then analyzed and compared amongst the groups.

Results: 41 females (85.4%) and 7 males (14.6%) were identified with an average age of 39.5, an average weight loss of 64.5 kg, and an average BMI of 30.4 kg/m² at time of surgery. Mild fluid accumulation was found in 20 patients (41.7%), moderate accumulation in 13 patients (27.1%), and severe accumulation in 15 patients (31.2%). When the operative BMI ranges were evaluated, the incidence of severe fluid accumulation was as follows: <18.5 kg/m² (0%), 18.5-24.9 kg/m² (26.7%), 25.0-29.9 kg/m² (20%), 30.0-39.9 kg/m² (40%), >40.0 kg/m² (13.3%). The average weight of tissue removed increased 49.8% between the mild and moderate fluid accumulation groups and increased 14.3% between moderate and severe fluid accumulation groups.

Conclusion: Based on this sample population: 1. BMI at time of surgery is not associated with incidence of increased fluid accumulation. 2. Weight of excised tissue is associated with incidence of increased fluid accumulation. 3. Other epidemiological factors either showed no association or were too limited to analyze.
Maternal Glucose Correlation with Spina Bifida Related Genes

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Sponsored by:  Hope Northrup, MD, Department of Pediatrics
Supported by:  NIH 7P01HD035946-07
Key Words:  Spina Bifida, Glucose Uptake, 2-NBDG, Genotypes

Spina bifida is a multifactorial common birth defect with both environmental and genetic causes. Previous studies have shown that maternal hyperglycemia increases the risk of having a child with spina bifida. In addition, we showed a significant association between polymorphic variants in GLUT1, HK1, and LEPR genes and spina bifida. We speculated these variants may lead to a change of biologic activities of these genes' products and subsequently increase the risk for spina bifida development. In this project, we studied the biologic activities of these three variants in glucose uptake and glucose metabolism by a cell culture system. We aimed to compare glucose uptakes of patients who are homozygous for the common variant, heterozygous, and homozygous for the rare variant for each of the three genes. The white blood cells from the patient’s anti-coagulated whole blood were isolated and used for glucose uptake utilizing a fluorescent glucose, 2-NBDG, under high, normal glucose or sucrose treatments. In addition, RNAs were isolated from the treated cells for RT-PCR to reveal the expression of the three genes. Ratios comparing the uptake in high glucose conditions versus low glucose conditions were calculated. Significant differences were observed between different genotypes that suggest these genotypes correlated to the rate of glucose uptake in the patient cells. A patient homozygous for the common variants had much higher glucose uptake than that of a patient homozygous for the rare variant. There was also a significant difference when observing glucose uptake between the patients and their mothers with different genotypes.
.Localization and Densities of the Parkinson’s Disease Associated Proteins And Cytokines to Specific Areas And Structures in the Brain Following Lipopolysaccharide Treatments in Rats.

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Sponsored by: Roger J. Bick, PhD (Pathology) and Mya C. Schiess, MD (Neurology)
Supported by: Kanaly Foundation for Parkinson’s disease research
Key Words: Lipopolysaccharide, cytokines, Parkinson’s disease, tau, synuclein, ubiquitin

The onset of Parkinson’s disease (PD) and subsequent neurodegeneration has been linked to inflammatory episodes, such as are found in chronic and severe infections. An animal model of infection has been used in which lipopolysaccharide (LPS), a bacterial endotoxin, is injected into rats with subsequent removal of tissues for pathologic studies. We injected rats with high doses of LPS that were determined via cell culture studies, to sustain aggregations and disruptions of the PD associated proteins tau, alpha-synuclein and ubiquitin and induce the synthesis and release of cytokines. The brains were removed, and the olfactory bulb and substantia nigra areas were separated, fixed and sectioned for subsequent deconvolution fluorescence microscopy. Sections were probed with antibodies to tau, alpha-synuclein and ubiquitin and tagged secondary antibodies were added to facilitate visualization of the proteins. Specific cytokines that have been reported as being associated with PD and neurodegeneration were also visualized, and the co-localizations of the proteins and cytokines to specific areas and structures of the brain sections were mapped. Image reconstructions were made and 3D models of the stacked sections were generated. Images demonstrated that a 24 hour LPS treatment caused specific proteins and cytokines to relocate from a perinuclear position to a more punctuate distribution, while treatment for 48 hours resulted in a further relocation of specific cytokines/proteins to their prior, perinuclear site, while others remained in a diffuse pattern. This research points to particular cytokine and protein patterns as markers in neurodegeneration and as potential diagnostic adjuncts.
Dysfunction of the Nitric Oxide Pathway in the Chronic Phase of Spinal Cord Injury

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Sponsored by: Raymond J. Grill Ph.D. Department of Neurosurgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15; NINDS RO1 NS049409-01A2
Key Words: Spinal Cord Injury, Neuronal Nitric Oxide Synthase, Activating Transcription Factor 3

Spinal cord injury (SCI) initiates a broad biochemical response that contributes to secondary tissue pathologies. Nitric Oxide (NO) is a diffusible signaling molecule capable of exerting both neuroprotective and detrimental effects on the CNS following trauma. NO, produced by neuronal nitric oxide synthase (NOS), is a potent modulator of neuronal and non-neuronal activity. Injury causes an increase in NO production, reaching a peak by 14 days post-SCI, fueling oxidative stress. Oxidative stress leads to the expression of stress-inducible factors such as ATF3. ATF3-labeling has also been used to identify neurons undergoing oxidative stress that are “at risk” for death. However, neither nNOS nor ATF3 expression has been examined in the chronic phase of SCI. We used immunohistochemistry to determine the time course of ATF3 and nNOS expression 24 h, 7 days, 1 and 10 months after SCI. ATF3 expression peaked at 3 days and persisted for two weeks before declining one month after injury, becoming virtually undetectable by 10 months. SCI-induced nNOS expression peaked at 7 days and then continued to decline out to 10 months. These results are intriguing as it suggests an ongoing pathology in which either nNOS-expressing neurons continue to die or lose expression of nNOS long after the initial spinal insult. nNOS’s role in both normal and injured spinal cord is poorly understood. However, it is thought to play a regulatory role in both neurosensory and motor functions. A progressive loss of this modulatory pathway may have profound effects on such SCI-related pathologies as neuropathic pain.
ABSTRACT

Identification of causative bacteria in diabetic foot infections by 16S rRNA sequencing

MATTHEW JORDAN The University of Texas at Houston Medical School Class of 2010

Sponsored by: Dr. Catherine Ambrose Ph.D., Department of Orthopaedic Surgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: 16S rRNA, diabetic foot

Diabetes mellitus is increasing by epidemic proportions resulting in end-organ damage due to many years of hyperglycemia presenting a major burden of health care worldwide. Foot ulceration is the most common major end point among diabetic complications. Currently diabetic foot infections are diagnosed based on culture tests of tissue samples. In the majority of the cultures, the infection is deemed to be polymicrobial, which makes the infections more difficult to treat and can be more difficult to diagnose through culture. Thus, standard laboratory cultivation and identification methods may be inadequate to study the bacterial flora. Studies with molecular techniques, such as 16S rRNA analysis using broad-range primers, offer an alternative approach to identify bacteria and assess their diversity. This technique affords many advantages: it is capable of detecting bacteria that are present in very small numbers and it can be used for non-culturable bacteria. Thirteen tissue samples were collected from diabetic patients who have been determined by their physicians to have evidence of foot infection. Using primers for the conserved regions of the bacterial 16S rRNA gene, PCR was performed and DNA sequence analysis was used to determine the identity of the infectious agent.
ABSTRACT

Vascular Contrast Extravasation on 40-Slice Multi-Detector Row Trauma CT of the Torso: Implications for Clinical Management

DANIEL S. KIEVLAN  The University of Texas at Houston Medical School  Class of 2010

Sponsored by:  O. Clark West, MD, Department of Diagnostic and Interventional Imaging
Supported by:  John S. Dunn Foundation
Susan D. John, MD, Department of Diagnostic and Interventional Imaging
O. Clark West, MD, Department of Diagnostic and Interventional Imaging

Key Words:  vascular contrast extravasation, computed tomography, hemorrhage, blunt torso trauma

Traditionally, the appearance of vascular contrast extravasation (VCE) on CT of the chest, abdomen or pelvis in a patient warrants immediate treatment by surgery or angiographic embolization. Current generation 40 and 64 slice multi-detector row CT scans may be capable of depicting smaller degrees of VCE, potentially detecting minor hemorrhages that require no treatment. In this project, we reviewed consecutive CT scans of the chest, abdomen, abdomen/pelvis, and chest/abdomen/pelvis performed on the Siemens Sensation 40 CT scanner located in the Emergency Center of MHH-TMC from October 1, 2005 to June 30, 2007. 4971 cases of blunt trauma were found. 153 patients (3.1%) had written reports diagnosing VCE. There were 188 instances of VCE; 127 patients had a single site of VCE, 17 had two sites, and 9 had three sites. Most common locations of VCE injury were: spleen (56 instances; 30% of total instances), pelvis (32; 17%), soft tissues/intramuscular areas (30; 16%), and liver (22; 12%). Other sites accounted for 48 instances, including kidneys (11; 6%), adrenal glands (9; 5%), retroperitoneum (8 instances; 4%) and mesentery (7; 4%). For the most common locations (140 instances), review of medical records revealed that splenic injuries most often required treatment. Of spleen injuries, 7 (13%) received non-operative treatment, 25 (45%) arteriographic, 28 (50%) surgical, and 5 (9%) both arteriographic and surgical. Of pelvis injuries, 7 (22%) non-operative, 17 (53%) arteriographic, 13 (41%) surgical, and 5 (16%) both arteriographic and surgical. Of soft tissue/intramuscular injuries, 16 (53%) non-operative, 6 (20%) arteriographic, 3 (10%) surgical, and 2 (7%) both arteriographic and surgical. Of liver injuries, 4 (18%) non-operative, 8 (36%) arteriographic, 9 (41%) surgical, and 3 (14%) both arteriographic and surgical. Based on initial analysis, we conclude that most injuries in the spleen, pelvis and liver demonstrating VCE still are treated urgently. VCE in the muscles and soft tissues are less likely to require therapy. We are currently analyzing injury morphology and patient clinical status to develop a prediction rule to select treatment for patients.
ABSTRACT

Bone Density Assessment Using DXA for Pediatric Populations

LAUREN A. LaROCHE The University of Texas at Houston Medical School Class of 2010

Sponsored by:  Catherine Ambrose, PhD, Department of Orthopedics
Supported by:   Dr. Dhiren Sheth, Department of Orthopaedics
Key Words:    Bone Mineral Density (BMD), DXA, Osteogenesis Imperfecta (OI)

Bone mineral density is routinely measured by a dual energy x-ray absorptiometry, or DXA, machine, where several makes (pencil vs. fan beam) and models by different manufacturers currently are available. Adult reference databases are provided in order to determine an adult’s bone mineral density in comparison to the age of peak bone mass and age matched peers. However, only the newest machines provide reference databases for pediatric populations. Due to the variability in results produced by different machines, each machine needs its own database to perform accurate statistical analyses, as algorithms formulated to eliminate variability between the machines are highly imprecise.

At our institution, pediatric patients with certain metabolic disorders such as Osteogenesis Imperfecta are tracked longitudinally to monitor their disease progression. We cannot compare these patients to a normal population, as a pediatric reference database does not exist for our machine.

The objective of this project was to determine bone mineral density using the Hologic QDR 4000 at 3 standard measurement sites for children ages 4-18 in order to create a normals reference database. The manufacturer recommends that at least 20 subjects per decade from both sexes in each of the ethnicity categories (Caucasian, Hispanic, Asian, and Black) be included in a reference database (n=320). To date 65 patients have been scanned. Preliminary analysis demonstrates that BMD increases with age through the years studied. At this point we do not have enough data to analyze the differences due to sex and ethnicity.
Whole Brain White Matter Integrity and Impulsivity in Cocaine Dependence

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Sponsored by: Joel L. Steinberg, MD, Department of Psychiatry and Behavioral Sciences
              F. Gerard Moeller, MD, Department of Psychiatry and Behavioral Sciences

Supported by: The Bernard Saltzberg Summer Research Fellowship

Key Words: diffusion tensor imaging, segmentation, cocaine dependence, impulsivity

Rationale: Numerous studies have identified cognitive changes and impulsive behaviors in cocaine-dependent persons. Previous neuroimaging studies have found abnormalities in brain white matter (WM) structures in cocaine-dependent subjects. Design and Methods: In this study, fifteen cocaine-dependent subjects and fifteen age-matched controls underwent diffusion tensor imaging (DTI) in a 3.0 T MR scanner. For analysis, brain tissue was segmented into cerebrospinal fluid, gray matter, and WM; diffusion measures of fractional anisotropy (FA), mean diffusivity (MD), transverse ($\lambda_T$) and longitudinal ($\lambda_1$) eigenvalues, and fractional volume were calculated for WM. Subjects completed the Immediate Memory Task/Delayed Memory Task (IMT/DMT) as a measure of impulsive behavior. A subset of subjects also completed the Iowa Gambling Task (IGT) as a measure of decision-making and the Barratt Impulsiveness Scale (BIS-11) to assess impulsivity. Results: Cocaine-dependent persons exhibited significantly lower WM FA and proportionally less whole brain WM than did controls; a trend existed for the BIS-11 nonplanning subscale, with cocaine-dependent persons exhibiting more nonplanning. Cocaine-dependent subjects showed poorer choices and impaired learning on the IGT, replicating previous findings. Within controls, DTI metrics did not significantly correlate with behavioral and cognitive measures. Within the cocaine group, IMT commission errors, which indicate impulsive behavior, correlated significantly with WM $\lambda_1$; also, the BIS-11 motor subscore correlated significantly with $\lambda_1$, fractional volume, and MD. Conclusions: These results suggest that alterations in brain WM may account for some cognitive and behavioral deficits related to impulsivity seen in cocaine dependence. Analysis of prefrontal WM is ongoing and will be presented.
ABSTRACT

Determining Risk Factors for Prediction of Vancomycin Failure in Patients with MRSA Bacteremia

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Sponsored by: Audrey Wanger, PhD, Department of Pathology and Laboratory Medicine
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Supported by: Dr. Audrey Wanger, PhD, Department of Pathology and Laboratory Medicine
The University of Texas at Houston Medical School

Key Words: MRSA, Vancomycin

There has been increasing debate regarding the efficacy of vancomycin in treating MRSA bacteremia. Vancomycin was FDA approved in 1958, several years prior to the 1st documented case of MRSA. As such, the demonstration of vancomycin efficacy for MRSA bacteremia that would result in FDA approval today is lacking. Thus, understanding the relationship between vancomycin treatment failures and microbiological characteristics of the organisms is paramount in defining the role vancomycin has in the treatment of MRSA bacteremia.

162 consecutive MRSA blood culture isolates from patients admitted to Memorial Hermann Hospital from August 2005 to May 2007 were obtained. Vancomycin minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) were determined by using broth microdilution described by the CLSI. Organisms were screened for heteroresistant vancomycin intermediate Staphylococcus aureus (hVISA) phenotype utilizing the Etest® macromethod with vancomycin and teicoplanin on BHI agar plates.

The MIC₅₀/₉₀ of the isolates were 0.5/1 μg/ml. Only one strain was found to have a MIC of 2μg/ml. The vancomycin MBC₅₀/₉₀ of the isolates were 0.5/2 μg/ml. 10/162 (6%) isolates were found to have a vancomycin MBC/MIC ratio of ≥ 8. 14/162 (9%) of all isolates were suggestive of the hVISA phenotype.

The microbiological characteristics of MRSA isolates were found to be consistent with previous reports. The hVISA phenotypes accounted for 9% of the isolates. Correlation with clinical outcomes is warranted.
ABSTRACT

Effect of Prostaglandin E2 on Gastric Matrix Metalloproteinase Production

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Sponsored by: Emily K. Robinson, MD, Department of Surgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: MMP, PGE2, SC560, gastric injury

Introduction: Matrix metalloproteinases (MMP) are endopeptidases that degrade extracellular components and contribute to gastric injury in a model of lipopolysaccharide (LPS) induced endotoxemia. We have previously shown that LPS causes gastric injury and increases MMP-2 activity in the gastric mucosa. Inhibition of inducible nitric oxide synthase (iNOS) attenuates the LPS-induced expression of gastric MMP-2. The purpose of this study was to investigate how prostaglandin E2 (PGE2) regulates changes in the expression of MMP-2 in the gastric mucosa in the presence and absence of LPS.

Methods: Sprague-Dawley rats (N ≥ 4/group; ANOVA) were given the selective COX-1 inhibitor SC560 (4mg/kg IP) or saline 1 hour prior to administration of LPS (20mg/kg IP) or saline. Exogenous PGE2 (0, 30, or 90 ug/kg) was given orally 30 minutes prior to and 9 hours after LPS. The animals were sacrificed 24 hours after LPS. Gastric luminal fluid accumulation was measured along with gastric pH and gastric luminal nitrate concentration. Gastric mucosa was harvested and protein production of MMP-2 and its inhibitor (TIMP-2) were assessed using Western blotting.

Results: The administration of LPS significantly increased MMP-2 protein production. SC560 significantly decreased this LPS-induced expression, while the administration of PGE2 further decreased expression in a dose-dependent manner. LPS significantly decreased the expression of TIMP-2, while administration of PGE2 further decreased expression. Gastric luminal nitrate concentrations were significantly decreased by the administration of PGE2 as determined by Griess reaction. Neither SC560 nor PGE2 had any effect on gastric luminal fluid volume or pH.

Conclusions: The oral administration of PGE2 decreases the expression of MMP-2 and TIMP-2 in the gastric mucosa and decreases the concentration of gastric luminal nitrates. This data seems to suggest that PGE2 plays a protective role in the gastric mucosa through regulation of MMP-2 expression, possibly through its effect on nitric oxide concentration.
PKC Activity and CPI-17 Phosphorylation in Edema-induced Reduction of Myosin Light Chain Phosphorylation in the Small Intestine

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Sponsored by: Karen Uray, PhD, Department of Pediatric Surgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: CPI-17, Intestinal Edema, Myosin Light Chain Phosphotase

Intestinal interstitial edema, often associated with abdominal surgery and trauma resuscitation, has been shown to reduce intestinal motility via decreased intestinal smooth muscle myosin light chain phosphorylation (Uray 2006). Preliminary data showed no changes in myosin light chain kinase activity in edematous intestine compared to normal intestine. A decreased phosphorylation of MYPT1, the regulatory subunit of myosin light chain phosphatase, was observed in the edematous intestinal smooth muscle compared to non-edematous tissue suggesting that intestinal edema affects myosin light chain phosphatase activity. CPI-17 inhibits myosin light chain phosphatase when it becomes phosphorylated (Murthy 2006), and PKC has been shown to phosphorylate CPI-17 (Walsh 2006). We hypothesize that intestinal edema reduces PKC activity so that CPI-17 phosphorylation is decreased resulting in decreased inhibition of the MLCP. Intestinal edema was induced in a rat model by a combination of mesenteric venous hypertension and resuscitation fluid administration with sample collection at 0, 0.5, 2, and 6 hours after surgery. A PKC assay kit (Upstate) based on phosphorylation of a specific PKC substrate peptide with PKC and $^{32}$P-ATP was used to measure PKC activity. Western blotting will be used to measure the phosphorylation of CPI-17 normalized to GAPDH. The PKC assay kit showed a significant decrease in phosphorylation in the edematous samples versus the control as well as an increase in PKC activity at the 6 hours compared to 2. Western blotting results to test the phosphorylation of CPI-17 have yet to be completed. Although the phosphorylation of the CPI-17 results have not been completed, the PKC data indicate there is a reduced phosphorylation in edematous intestine. This would support the hypothesis that CPI-17 phosphorylation is decreased resulting in decreased inhibition of the MLCP; thus, decreased myosin light chain phosphorylation.
ABSTRACT

Functional MRI Study Of Working Memory In Cocaine Users

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Sponsored by:  Joel L. Steinberg, MD, Department of Psychiatry & Behavioral Sciences
Supported by:  Dr. Bernard Salzberg Research Scholarship Fund
Key Words:  functional magnetic resonance imaging, working memory, cocaine

Background:  While there has been extensive study into the types of deficits produced by cocaine, there has been less research into the specific regions of the brain that are directly affected by cocaine.

Objectives:  The purpose of this study was to use functional magnetic resonance imaging (fMRI) to determine whether cocaine users would differ from non-cocaine users while performing a working memory task.

Methods:  Nine cocaine-using subjects and 5 non-cocaine using controls underwent fMRI scanning using a 3T scanner. While in the scanner, subjects performed immediate and delayed memory tasks (IMT/DMT). Each task was performed in an alternating block of IMT followed by DMT with varying difficulty. The sequence of difficulty was randomly determined and was parametrically varied using three, five, and seven digits.

Results:  The fMRI time series was band-pass filtered, and random effects analysis using SPM2 was performed on all subjects. Greater activation was found in cocaine users compared to normal subjects during DMT compared to IMT. During the easiest task—three digits—there was greater activation in the thalamus extending into the cerebellum, parietal, and frontal lobes. In the most difficult task—seven digits—greater activation was found in the medial inferior frontal gyrus. Significant differences were found between groups for IQ scores and ages (p=0.05). Regression analysis determined that there were no significant correlations with age or IQ in areas that were significantly different between groups.

Conclusions:  Findings of greater activation in cocaine-users versus controls is consistent with previous studies involving stimulants such as MDMA.
ABSTRACT

Renal Function in AIDS Patients: Is Dose-Dependent Ritonavir Administration a Co-Factor in Tenofovir-Associated Nephrotoxicity?

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Sponsored by: Roberto C. Arduino, MD, Department of Internal Medicine, Infectious Diseases
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: Pharmacokinetics, nephrotoxicity, drug interactions, therapeutic drug monitoring

Protease inhibitors, especially ritonavir, are potent inhibitors of drug secretion in the proximal renal tubule. It has been hypothesized that tenofovir-related nephrotoxicity may be worsened by protease-induced inhibition of its efflux mechanism. This study aims to identify if there is a dose-dependent interaction between ritonavir and tenofovir resulting in renal toxicity.

As part of a prospective, randomized controlled trial of once daily boosted protease inhibitor-based antiretroviral therapy in naïve patients, 76 patients have been assigned to Truvada (emtricitabine 200mg/tenofovir 300mg) once daily with either atazanavir 300mg/ritonavir 100mg or fosamprenavir 1400mg/ritonavir 200mg. The analysis of repeated measures of glomerular filtration rate (GFR) over time thus compares ritonavir 100mg versus 200mg in a potential interaction with tenofovir. GFR was estimated by simplified MDRD (modification of diet in renal disease) study equation.

The sample comprised 76 patients with 1 to 11 visits with an average of follow-up time of 83.5 weeks. The time of observation did not significantly differ by treatment arm. The slope (GFR over time) was measured to determine if it differed over treatment arms. The slope is negative (-0.039) for the ATV arm but almost flat (0.0022) for the fAPV arm.

In this study cohort there is no significant decline in GFR as measured by MDRD in the 100mg ritonavir arm compared with the 200mg arm. This suggests that increased ritonavir dosing at these levels is not associated with a steeper rate of decline in renal function in patients receiving tenofovir.
ABSTRACT

Pathogenesis of Enterotoxigenic Escherichia coli Diarrhea
Inflammation as a Mechanism of Pathogenesis

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Sponsored by: Dr. Herbert Dupont MD Department of Internal Medicine
Supported by:  Dr. Dupont MD Department of Internal Medicine
Key Words:   ETEC Inflammatory response

Purpose:   This study will screen fecal samples from patients with travelers’ diarrhea due to ETEC to determine which ETEC virulence factor is associated with inflammatory exudation (positive for IL-8 and IL-1B). The strains identified plus an equal number of ETEC not associated with inflammatory exudates will be further studied for induction of cytokine response in a tissue culture model, which will enable us to define the probable ETEC virulence property or properties associated with the inflammatory response.

Methods:   1. Fecal samples from patients with travelers’ diarrhea acquired in India, Kenya, Guatemala and Mexico studied. Samples will be selected when ETEC is the sole pathogen detected.
2. Measurement of IL-8 and IL-1b by commercial ELISA in the stools collected from patients with ETEC diarrhea and control population (160 stool samples).
3. Induction of IL-8 and IL-1b from HCT-8 Tissue Culture Cells
4. Study of colonization factor antigens for the study ETEC strains
5. Study for presence of Tia- and Tib-mediated adherence/invasion of ETEC strains and correlated with production of inflammatory mediators (fecal IL-8 and IL-1b)
6. Role of flagella/motility on cytokine secretion by ETEC strains
7. Statistical Methods

Fecal cytokine concentrations will be compared by the Kruskal-Wallis nonparametric group comparison. Mean and media elicited IL-8 levels from HCT-8 cells to infection will be reported. Significant amounts of IL-8 elicited in the tissue culture model will be defined as IL-8 levels of >100 pg/ml. The frequencies of bacteria invasive to toxin type will be compared using chi-square test. Fisher's exact probability test will be used when the number of observations in a fourfold table was too small for a chi-square test.

Results:  Results are still pending

Conclusions: If we find that there is a statistically significant difference presence of IL-8 in the stools of those infected with ETEC vs Controls then this would suggest that there is an inflammatory response to ETEC.
ABSTRACT

Role of Free Radicals Following Chloroprocaine-Mediated Neurotoxicity in Conscious Rats

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Sponsored by: Marie-Francoise Doursout, PhD, Department of Anesthesiology
Supported by: Marie-Francoise Doursout, Department of Anesthesiology
Key Words: Local anesthetic; intrathecal administration; chloroprocaine; behavioral functions, tail-flick; rats

Neurological defects after apparent intrathecal injection of chloroprocaine, a local anesthetic, intended for epidural administration, created concerns about the potential neurotoxicity of chloroprocaine and its preservative sodium bisulfite. Therefore, experiments were assessed using a relevant histological model—the chronically instrumented rat—to investigate the intrathecal neurotoxicity of these 2 compounds alone and in combination. Under isoflurane anesthesia, a PE-10 catheter was surgically inserted at the level of T13–L1 to a position 2 cm caudal for intrathecal drug administration at the level of the lumbar enlargement. Following full recovery from surgery, animals were divided into 3 groups. Group 1 animals were injected with chloroprocaine i.t at 1%, 2%, 3%; Group 2 animals with sodium bisulfite at 1%, 2%, 5% and Group 3 animals with combined treatments. Following i.t drug administrations, behavioral functions (e.g. somnolence, biting and motor function—ability to walk) were recorded at baseline, after drug administration and once a day for 7 days. To record sensory function, baseline tail-flick was assessed immediately before and after drug administration, and once a day for 7 days. After sensory assessments, animals were sacrificed, the spinal cord and nerve roots were rapidly dissected out and maintained at -70°C for future assays. Our data show that rats treated with 1% chloroprocaine have peak behavioral sensation impairment at around 2 days post treatment and failed to return to control levels after 7 days. 2% and 3% chloroprocaine treated animals peaked at 4 days and also didn’t return to control levels. In contrast, animals treated with different concentrations of sodium bisulfite show a lesser degree of impairment, but also failed to return to baseline. Furthermore, no spinal cord damage was recorded using H&E staining in rats treated with chloroprocaine. In conclusion, our preliminary data show that chloroprocaine has a greater effect on behavioral sensation than does sodium bisulfite. However, additional experiments are needed to value the effects of chloroprocaine combined with sodium bisulfite.
Dietary Nucleotides and the Skeletal System in a Mouse Model of Accelerated Aging.

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Sponsored by: Anil D. Kulkarni, PhD, Department of Surgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases,
5T35 DK007676-15
Key Words: Dietary nucleotides, aging, bone, BMD, HU

Dietary nucleotides (NT) act as biological response modifiers (BRM) in animals and humans. Anti-orthostatic hindlimb weight unloading (HU) of rodents causes immune dysfunction, has adverse physiologic effects associated with space flight, and acts as an accelerated aging model. We investigated the effects of HU and NT on the skeletal system to maintain and restore bone mass and density in aging. Eight to ten week old Balb/c mice were subjected to HU for one week with control chow and NT-supplemented chow. Bones were removed for density determinations and structural analysis using Micro Computed Tomography (μCT) and Dual-Energy X-ray Absorptiometry (DXA). μCT analysis showed several differences in the distal femur region. Bone Mineral Density (BMD) decreased 5.9% and Bone Volume Percentage (BV%) decreased 12.1% in HU control diet (Ci) group compared to non-HU control (C) group. The HU NT (Ri) group BMD increased by 11.8% and BV% increased by 28.4% compared to Ci group. μCT showed a 28.9% increase in trabecular number and a 25.3% decrease in trabecular spacing in Ri group compared to R group. DXA analysis showed an increase in Bone Mineral Content in Ri group of 8.2% and 20.5% compared to R and Ci groups respectively. In addition to our previous observations that NT maintain and improve immune function, these results show that NT may have positive effects on mesenchymal bone marrow cells and benefit the skeletal system. Thus, NT may have a significant beneficial role and application in aging as well as space flights.
ABSTRACT

Height and Body Mass Index Measurements in Children with Myelomeningocele

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Sponsored by:  Allison Scott, MD, Department of Orthopaedics
Supported by:  Shriners Hospitals for Children, Houston, Texas
Key Words:  Myelomeningocele, BMI

Purpose:  Myelomeningocele is associated with joint contractures, leg deformities, scoliosis and a decreased level of ambulation, all of which make measuring height difficult in this population. Myelomeningocele and obesity have also been linked in the past. The aim of the present study was to measure the body mass index in children with myelomeningocele and to determine if height in this population can be estimated using other more easily obtainable measures.

Methods:  Standing height and/or supine height, sitting height, arm span, and weight were obtained on thirty-six children (ages 5.6 to 18.5 years) with a diagnosis of myelomeningocele. Body mass index was calculated using the measured heights and weights.

Results:  36.1% of the study population was overweight (above the 95th percentile BMI for age), and 55.6% were overweight or at risk for overweight (above the 85th percentile BMI for age). Neither arm span (r=.776) nor twice the sitting height (r=.830) were highly correlated with actual height. Neither level of lesion nor gender had a direct relationship with height. Linear regression was performed accounting for arm span, sitting height, and age and an equation was calculated (r=.898) to best predict height.

   Height (cm) = 10.61 + (1.02 x Sitting Ht) + ( 0.40 x Arm span) – (0.15 x Age)

Conclusion:  Obesity is common in the pediatric population with myelomeningocele. Unfortunately simple measures such as arm span or sitting height do not accurately estimate heights. Height can be better estimated by a linear regression formula calculated in this study; however due to its complexity, supine height measurements may be easier to obtain and use. Significance: Children with myelomeningocele should have their body mass index calculated to assess obesity. Obtaining a height measurements requires accommodating deformities and measuring in the supine position or using an equation combining arm span, sitting height, and age.
ABSTRACT

Laser Bleb Revisions of Tube Shunts in Uncontrolled Glaucoma Patients

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Sponsored by: Robert Feldman, MD, Department of Ophthalmology
Supported by: The University of Texas at Houston Medical School
Key Words: Glaucoma, IOP

Glaucoma is an ocular disease in which there is an elevated intraocular pressure (IOP). A chronically elevated IOP can result in optic nerve damage and eventually blindness. Installation of tube shunts is a surgical intervention that can be taken when glaucoma is uncontrolled by maximal levels of medication. If, however, the shunt fails to lower the IOP to an acceptable level, there is no standardized and efficacious alternative method of therapy. This study attempts to determine the efficacy of lasering the bleb of a failed tube shunt. This is a retrospective case-series in which 7 uncontrolled glaucoma patients received the laser bleb revision. The IOPs in all the eyes that received the revision all decreased from a mean of 33.7 to 22.44 mmHg, while the average number of IOP-lowering medications dropped from an average pre-revision value of 3 to a post-revision value of 1.86. The normal cut-off for a normal and abnormal IOP is 21 mmHg, which shows that the average IOP of this patient population is still elevated, but the laser bleb revision was shown to cause a significant decrease in the number of IOP-lowering medications and a highly significant decrease in IOPs. Lowering the IOP in an eye, even to a still elevated level, will delay onset of optic nerve damage and blindness. Though the current study has a limited sample size, the results call for further research concerning the efficacy of this treatment for uncontrolled glaucoma patients.
ABSTRACT

Neural Stem Cell Therapy for Traumatic Brain Injury

LEEANN E. SLOAN  The University of Texas at Houston Medical School  Class of 2010

Sponsored by: Charles S. Cox, Jr. M.D., Department of Pediatric Surgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: Traumatic Brain Injury (TBI), Neural Stem Cells (NSCs)

Introduction: Traumatic Brain Injury (TBI) frequently results in devastating and prolonged morbidity. We studied the use of Neural Stem Cells to treat TBI.

Methods: The neural stem progenitor cells (NSCs) were characterized by flow cytometry and placed stereotactically into female Sprague Dawley rats one week after undergoing a controlled cortical impact injury. Immunohistochemistry was used to identify cells located in the brain at 48 hours and 2 weeks after administration. Motor function was assessed using the neurological severity score, foot fault, rotarod, and beam balance. Cognitive function was assessed using the Morris Water Maze learning paradigm.

Results: Immunohistochemistry analysis revealed that 1.5-3% of infused cells remained in the tissue at 48 hours and two weeks post placement. Rotarod motor testing revealed improvement among NSC treated rats (P=0.04). All other motor and cognitive evaluations were not significantly different compared to controls.

Conclusion: Placement of NSCs led to the cells incorporating and remaining in the tissues two weeks after placement. Motor function tests revealed improvements in the ability to run on a rotating rod; however other motor and cognitive functions were not improved by NSC therapy at this time point. Future work includes increasing transplanted cell number and behavioral testing at lengthened time intervals.
ABSTRACT

Producing a Scale for Tear Film Images Correlated with Clinical Tests for Dry Eye

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Sponsored by:  Richard Yee, MD, Department of Ophthalmology
Supported by:  Richard Yee, MD, Department of Ophthalmology
Key Words:  Dry Eye, Tear Film, ConfoScan 4

Background:  The tear film is a composite layer made up of a mucin component, which rests on the epithelial surface, an aqueous component above it, and an oily outer layer. The mucin component helps spread the aqueous layer evenly over the cornea and conjunctiva. It also coats small foreign bodies so they can be easily removed by blinking. The aqueous layer consists of a dilute solution of salts, minerals, and dissolved organic materials, and it represents 90% of the thickness of the tear film. This layer hydrates the cornea, and flushes contaminants from the eye. The outermost layer is the lipid layer. It contains components secreted by the meibomian glands that serve as a barrier against tear evaporation and provides lubrication to the ocular surface. Many factors contribute to dry eye, including reduced blinking rates, environmental factors, blepharitis, contact lenses, and many others.

Purpose:  Develop a scale for grading tear film images of dry eye patients.

Methods:  Using a noninvasive digital scanning slit microscope with a 20x lense (Nidek Confoscan 4), we imaged the tear film of patients with dry eye complaints. We also applied the standard clinical tests for dry eye: Lissamine green, Meibomian quantity and quality, and the basal tear test.

Results:  A ten-point scale for grading the tear film images captured by the ConfoScan 4 was developed based on the quantitative results from the standard clinical tests.
Glutamine as a Ligand-Dependent Activator of Peroxisome Proliferator-Activated Receptor-Gamma (PPARγ)

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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
Key Words:  Glutamine, PPARγ, PPRE, GW9662, ligand

Introduction: We have shown both clinically and in the laboratory that glutamine possesses gut protective effects under conditions of hypoperfusion and that protection is mediated by an increase in the anti-inflammatory transcriptional regulator, peroxisome proliferator-activated receptor-gamma (PPARγ). Once activated, PPARγ heterodimerizes with the retinoic acid receptor and binds to a PPARγ response element (PPRE) in the promoter of target genes. We hypothesize that glutamine activates PPARγ via a ligand-dependent mechanism.

Methods: Intestinal epithelial cells (IEC-6) were co-transfected with PPRE-luciferase promoter/reporter constructs and Renilla expression vectors. Cells were pretreated with increasing concentrations of glutamine ± GW9662 (a specific antagonist which irreversibly binds to the ligand-binding sites of PPARγ) then stimulated with 125 µM H2O2 to induce oxidant stress. Cell lysates were analyzed for PPRE luciferase activity as an indicator of PPARγ activation and normalized to Renilla expression. PPARγ nuclear activity was assessed by EMSA. Results are reported as mean ± SEM, average of 3 separate experiments.

Results: A concentration-dependent increase in luciferase activity was observed with the addition of glutamine under normal and oxidant conditions. This effect was abrogated by the specific PPARγ inhibitor, GW9662 and changes in luciferase activity correlated with changes in PPARγ nuclear activity.

Conclusions: Transcriptional activation of PPARγ by glutamine occurs via a ligand-dependent mechanism.
ABSTRACT

Mutations in *HVM-1* as a Cause of Familial Thoracic Aortic Aneurysms and Dissections and Other Vascular Diseases

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

Supported by: Doris Duke Charitable Foundation-Distinguished Clinical Scientist Award 20010851

Key Words: smooth muscle, aortic aneurysms and dissections, coronary artery disease, stroke

Smooth muscle cell (SMC) contraction is important in maintaining the integrity of vascular tissue and when impaired, has been shown to lead to life-threatening diseases such as thoracic aortic aneurysms and dissections (TAAD). Recently *HVM-1*, a gene encoding a SMC contractile protein, was found to lead to TAAD and other occlusive vascular disease when mutated. A review of clinical data and family histories on a cohort of five families with at least one member found to carry a heterozygous mutation in *HVM-1* was conducted to further illustrate the diversity of vascular diseases caused by mutation in this single, highly-conserved gene. Eleven individuals in the cohort were found to be positive for *HVM-1* mutation. Of these individuals, 100% had aortic and/or occlusive vascular disease as per medical records or personal interview. These diseases included TAAD, early-onset coronary artery disease, and stroke (defined as age of onset less than 55 years). Interestingly, 27% of individuals with mutation had patent ductus arteriosus. None of the family members found to be negative for mutation had any type of aortic or premature occlusive vascular disease. This data, in addition to that from earlier work by our group on a previous *HVM-1* cohort, is evidence of the wide array of vascular diseases that can result from mutations in *HVM-1*. Further work will investigate the mechanisms that lead to the development of such diseases in individuals possessing the altered gene product.
ABSTRACT

Tewametry and Corneometry Measurements Demonstrate Enhanced Hydration Effects in Subjects with Insulin-Dependent Diabetes Mellitus Treated with Ceramide Containing Multivesicular Emulsion

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Sponsored by: Adelaide A. Hebert, MD Department of Dermatology
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words: Diabetic feet, Xerosis, Tewametry, Corneometry

Patients with diabetes experience multiple foot complications, including up to an 80% incidence of xerosis and related changes including cracks, fissures, and erosions. Diabetics have impaired skin homeostasis, which is thought to be caused by a multitude of factors, including alterations of skin metabolism and complications such as vasculopathy and neuropathy. These predispositions highlight the importance of basic skin care measures in this population. An IRB approved study was designed to determine whether skin hydration in insulin-dependent diabetics can be enhanced by twice daily application of a ceramide containing multivesicular emulsion. Changes in the barrier function of the skin were assessed before and after application of the study cream using a Tewameter TM 210®, which measures transepidermal water loss, and a Corneometer CM 825®, which assesses moisture content of the stratum corneum. Thirty subjects with insulin-dependent diabetes mellitus were treated with a ceramide containing multivesicular emulsion twice daily for 14 days. Following treatment, subjects were assessed weekly over a 21 day period for improvement from baseline based on tewametry, corneometry, and investigator xerosis assessment scores. Preliminary data show increased moisture content of the stratum corneum as measured with a corneometer and improved investigator xerosis assessment scores after 14 days of twice daily application of the study cream. Twice daily application of a ceramide containing repair cream reduces xerosis of the feet in patients with insulin dependent diabetes mellitus by facilitating barrier function in the skin and may be a tool to help prevent diabetic foot complications.
ABSTRACT

The Effects of Alpha-Fluoromethylhistidine on Etinoipetal Axons/Rats

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Sponsored by:  David W Marshak, PhD, Department of Neurobiology and Anatomy
Supported by:  Grant number EY06472 from the National Eye Institute
Key Words:  Histamine, Dopamine, DOPAC, alpha-Fluoromethylhistidine, Retinopetal

Retinopetal axons run from the posterior hypothalamus to the retina via the optic nerve and terminate in the inner plexiform layer. These neurons fire action potentials and release histamine during the animal’s waking period, at night in the case of rats. Dopaminergic neurons are one of the major types of interneurons in the retina and they express receptors for histamine. In rats, dopamine synthesis is elevated in the presence of light and dopamine release follows a diurnal rhythm being reduced at night when the histaminergic neurons are most active. These experiments were designed to test the hypothesis that histamine inhibits retinal dopamine release in rat retinas. Two drugs were used to manipulate retinal histamine levels: alpha-fluoromethylhistidine (α-FMH) and L-histidine (L-his). α-FMH is an irreversible inhibitor of histidine decarboxylase (HDC) and L-his is the endogenous amino acid substrate of HDC. Adult Wistar strain rats were injected with α-FMH (20 mg/kg in sterile phosphate buffered saline [PBS]) and L-his (100 mg/kg in sterile PBS) to either irreversibly inhibit or stimulate HDC activity, respectively. The rats were euthanized 4 hours post-injection with a lethal dose of pentobarbital and perfused with cold PBS (4°C). The retinas were flash frozen in liquid nitrogen and using high performance liquid chromatography (HPLC), retinal levels of both histamine and 3,4-dihydroxyphenylacetic acid (DOPAC) will be measured. The measurements of retinal histamine and DOPAC levels are in progress and further experiments with different euthanization time points and drug concentrations will be performed.
The Molecular LVAD: Mechanical Unloading Increases Autophagy in Heart

KARI A. WELLNITZ  The University of Texas at Houston Medical School  Class of 2010

Sponsored by:  Dr. Heinrich Taegtmeyer, MD, DPhil, Department of Internal Medicine
Supported by:  National Institute of Diabetes and Digestive and Kidney Diseases, 5T35 DK007676-15
Key Words:  Autophagy, remodeling, LVAD

Introduction: We have observed Left Ventricular Assist Device (LVAD) implantation may result in the remission of heart failure obviating the need for heart transplantation. Mechanical unloading reduces markers of heart failure and is associated with a decrease in cardiomyocyte size. However, the molecular mechanisms resulting in improved cardiac function after mechanical unloading of the heart are not fully understood. Autophagy is an important intracellular pathway for the degradation and recycling of organelles and long-lived proteins by the lysosome. This process is essential for normal growth and remodeling and also in cellular responses to environmental stress. Simultaneous activation of the ubiquitin proteosome and of the mammalian target of rapamycin (mTOR) pathways has been observed in the unloaded heart, suggesting the presence of active remodeling involving both protein synthesis and degradation. However, the effect of mechanical unloading on autophagy in the failing heart is presently unknown.

Hypothesis: Autophagy is increased in the unloaded rat heart relative to the native heart.

Methods: Male Wistar rats underwent heterotopic heart transplantation and were sacrificed 7 days after surgery. Donor and recipient hearts were used for protein extraction. Immunoblotting was performed using anti-MAP LC3, anti-GAPDH, anti-phospho-p70 S6 kinase, and anti-Beclin1.

Results and future work: Markers of autophagy LC3-II and the Atg 5-Atg12 complex were significantly increased in the unloaded rat heart compared to the native heart 7 days post surgery, as were upstream positive autophagy regulators Beclin1 and phospho-p70S6K. These results suggest that autophagy is increased by mechanical unloading. We will further explore these preliminary findings by quantifying mRNA levels of autophagy genes Atg5 and Atg12 using RT-PCR. We will then use these data to investigate the molecular mechanisms contributing to autophagy during myocardial remodeling.
ABSTRACT

Second Place Winner of the Webber Prize for Student Research

The Role of Tumor Necrosis Factor-alpha, Complement C5, and Interleukin-6 in the Development of Mycobacterial Cord Factor Trehalose 6,6’-Dimycolate Induced Granulomatous Response

KERRY J. WELSH  The University of Texas at Houston Medical School  Class of 2010

Sponsored by: Jeffrey K. Actor, Ph.D., Department of Pathology and Laboratory Medicine
Supported by: NIH grants 1R21AI058247-1 & R01HL068537
Key Words: TDM, Granuloma, Inflammation, Lung, Tuberculosis

Background: Trehalose-6,6’-dimycolate (TDM) is a glycolipid component of the mycobacterial cell wall that causes immune responses in mice similar to natural Mycobacterium tuberculosis infection. Administration of TDM induces a granulomatous response with the production of proinflammatory cytokines. The roles of TNF-α, Complement C5, and IL-6 in the initiation and maintenance of granuloma formation in the TDM model are unknown.

Methods: Mice deficient in TNF-α, C5a, and IL-6, along with defined wild-type C57BL/6 controls, were tail vein injected with TDM, in a water and oil emulsion, and subsequently analyzed for histological response, and for production of chemotactic and proinflammatory mediators in lung tissue.

Results: Wild-type C57BL/6 mice demonstrated the formation of granulomas that correlated with increased production of IL-1β, IL-6, TNF-α, MIP-1α, IL-12p40, IFN-γ, and IL-10 protein and mRNA. The TNF-α knock-out mice failed to produce a histological response to TDM. Increases in cytokine and chemokine production following TDM administration were not detected in the TNF-α deficient mice. C5a -/- mice did not form cohesive granulomas and initially had decreased production of proinflammatory mediators. The IL-6 deficient mice appeared to initiate the formation of granulomas but failed to maintain them by 7 days post administration. The IL-6 knock-out mice also demonstrated decreased early production of proinflammatory mediators in comparison to the wild-type mice.

Conclusions: These data lead to the overall hypothesis that TNF-α is critically involved in the initiation of the granulomatous response, C5a is necessary for the formation of cohesive granulomas, and IL-6 is important for granuloma maintenance once established.
ABSTRACT

Cutaneous Leishmaniasis in Texas: A Northern Spread of Endemic Areas

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Sponsored by: Clay J. Cockerell, MD, Department of Dermatology, Division of Dermatopathology, The University of Texas Southwestern Medical Center, Dallas, Texas

Supported by: Clay J. Cockerell, MD, Department of Dermatology

Key Words: cutaneous leishmaniasis, phlebotamine sandfly, Leishmania mexicana

Background: Leishmaniasis, an infection caused by various species of Leishmania protozoa, is usually transmitted by the bite of phlebotomine sandflies. The clinical presentations are extremely diverse and dependent on a variety of host and parasitic factors. While rare in the United States, cutaneous leishmaniasis (CL) is endemic in south central Texas. At this time, no autochthonous cases of CL are known to have been reported in North Texas.

Methods: 9 cases of cutaneous leishmaniasis were identified histopathologically at a Dallas dermatopathology laboratory over the span of three years. A subsequent medical history review was conducted with Dallas-Fort Worth area dermatologists to collect patient demographics and travel histories.

Results: We report 9 autochthonous cases of CL obtained in North Texas residents. In all cases, diagnosis was confirmed by identification of Leishmania organisms upon histologic examination. In two reported cases, PCR revealed evidence of L. mexicana as the causative species. All reported cases were of Caucasian ethnicity, with an even gender distribution. Documented skin lesions did not appear to have an anatomic predilection. None of these patients had any travel history to areas known to be endemic for Leishmania.

Conclusion: Our cohort of 9 autochthonous cutaneous leishmaniasis patients from the North Texas indicates a shift in the areas where CL must be considered endemic. The reason for the expansion and northerly movement of Leishmania cases is unclear, but likely involves a shift in host-vector relationships. Physicians who live in newly endemic areas should be aware of the spread of cutaneous leishmaniasis and include this condition in the differential diagnosis of non-healing ulcerations.
ABSTRACT

A Randomized Clinical Comparison of the Disposable Laryngeal Tube Suction (LTS-D), The Esophageal Tracheal Combitube (ETC) and the Proseal Laryngeal Mask Airway (Plma) In Adult Patients

BRYAN YELVERTON  The University of Texas at Houston Medical School  Class of 2010

Sponsored by:  Dr. Carin Hagberg, MD, Professor, Department of Anesthesiology, Director of Neuroanesthesia and Advanced Airway Management

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

Key Words:  Esophageal Tracheal Combitube (ETC), Disposable Laryngeal Tube Suction (LTS-D), ProSeal Laryngeal Mask Airway (PLMA)

During the past decade, several pharyngeal airways have been introduced into clinical practice for airway management, such as the Laryngeal Mask Airway (LMA), the Cuffed Oropharyngeal Airway (COPA), the Esophageal Tracheal Combitube (ETC), and most recently, the Laryngeal Tube (LT). These airway devices have become very popular because of their ability to maintain an airway without perturbing the trachea, and can be used in patients without muscle relaxation and who are only lightly anesthetized. The LMA generally provides an adequate airway, but certain problems remain. (1) In 8-33% of LMA placements, more than one attempt is required. (2) It is sometimes difficult to advance the LMA without extending the neck (which is contraindicated in some patients). (3) The device does not protect the airway from aspiration of gastric contents. (4) It does not provide an airtight seal around the larynx (the usual pressures causing leakage of gas being 15-20 cm H2O). Consequently, the device functions poorly during positive-pressure ventilation. (5) The esophagus is included within the rim of the LMA in 10-15% of patients, directly exposing the esophagus to positive airway pressures. This often results in insufflation of the stomach and postoperative discomfort.

The purpose of this study is to evaluate a new supra-glottic airway device, the “Disposable Laryngeal Tube Suction” (LTS-D). We propose to test its ease of insertion, position within the airway, patency of drain tube and anatomic sealing properties during spontaneous ventilation in anesthetized patients in an attempt to address the problems involved with the use of the LMA listed above. The study device will be compared to the ProSeal Laryngeal Mask Airway (PLMA) and the Esophageal Tracheal Combitube (ETC).

Results: The results represent data from an on-going study from 57 out of 225 patients. Patient demographics were comparable between the 3 groups regarding age, and BMI, but differed in sex. The male:female distribution among participants in the ETC group (n=22) was 17:5, the LTS-D group (n=20) was 12:8, and the PLMA group (n=15) was 8:7. The results for the ETC, LTS-D, and PLMA groups include the following: average tidal volume (ETC, 0.456L ± 0.169, LTS-D, 0.493L ± 0.138, PLMA 0.463L ± 0.149), leak pressure (ETC, 21.57 ± 5.16, LTS-D, 24.61 ± 5.43, PLMA, 24.93 ± 5.00), peak pressure (ETC, 19.66 ± 4.36, LTS-D, 19.69 ± 4.48, PLMA, 16.15 ± 4.07), and duration of successful device placement (ETC, 34.38 sec ± 33.32, LTS-D, 27.00 sec ± 12.24, PLMA, 24.39 sec ± 11.06). The ETC had a failure rate of 22.7% which was significantly increased over the LTS-D (5%) and the PLMA (6.7%). (A failed attempt is defined as being unable to secure the airway in three attempts at placing the device). Post-operative complications were similar at 2 hours but had some notable differences at 24 hours. There is in increased incidence of difficulty swallowing in the ETC group (44%) compared with the LTS-D group (13%) and the PLMA group (17%). There is a decreased incidence of sore throat (PLMA 20%, ETC 56%, LTS-D 47%) and hoarseness (PLMA 8%, ETC 25%, LTS-D 20%) in the PLMA group.

Discussion: This is an on-going study and more data will be collected to achieve a statistically significant study comparing the use of these three supra-glottic devices.
INTERNATIONAL MEDICAL STUDENTS
The Timecourse of the Effect of Social Gaze Cues

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Sponsored by: Anne B. Sereno, PhD, Department of Neurobiology and Anatomy
Supported by: Graduate School of Biomedical Sciences  
The University of Texas at Houston Health Science Center
Key Words: autism, non-social gaze cues, social gaze cues

Autism is a brain disorder that impairs an individual's ability to think, feel, speak, and relate to others. The ability to follow another person's gaze is a basic and necessary behavior of normal human social interactions and its disruption may play a role in the profound social disability in autism. Extensive research examining non-social uninformative (exogenous) spatial attentional cues demonstrate that beginning around 100ms after cue onset, a subject is faster to respond to a target that happens to appear in the cued location compared to any other location (facilitation), and at longer intervals (e.g., 1000ms), is slower to respond to this same target location compared to any other location (inhibition of return). No research has defined the timecourse of social cues. In the present study, we examined the influence and timecourse of uninformative social cues. Subjects were asked to localize a laterally presented target (left or right key press). The target was preceded by a brief (33ms) centrally presented facial cue with eyes directed either to the left or right. The direction of the target was either congruent or incongruent with the preceding cue (equal probability). The stimulus onset asynchrony between cue and target varied from 33 to 1000ms. We found a significant facilitation of response as early as 33ms, with a peak at 100ms. Further, subjects continued to show a significant facilitation to the congruent target location 1000ms later. Thus, social cues elicit an earlier and longer lasting spatial attentional facilitation of key press than do non-social cues.
ABSTRACT

Window Managing System Facilitating EHR Multi-tasking

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Sponsored by: Jiajie Zhang, PhD, School of Health Information Science
Supported by: Graduate School of Biomedical Sciences
The University of Texas at Houston Health Science Center
Key Words: EHR, window managing, multi-tasking

The ability of handling multi-tasking by EHR systems is demanded by clinicians. Ordinary computer users always open lots of softwares at one time, e.g. E-mail client, Instant Messaging, Internet Browser, and Word Processor. They find it a time-consuming task to toggle between windows so to switch to their destined task. As EHR systems become stronger, same problem is happening to clinicians when they process information from multiple patients or multiple aspects of one patient at one time. Window managing system is to facilitate these processes.

There are different research directions in this particular field
1. Two dimensional window managing
2. Three dimensional window managing
3. Tabbed-view

My research is to evaluate the current situation of window managing systems and find out what is the underlined reason influencing human computer interaction. The significance of my research is to locate the cognitive level difference between the models causing different performance, and to help preventing interventions caused by inadequate window managing. The result can also benefit ordinary computer users

The methodology of this research is: First training the subjects so they will be familiar with those systems. Then each subject will participate three examinations: 1. Evaluating the speed of different systems. 2. Evaluating the accuracy of different systems. 3. Evaluating the capacity of different systems. The activity of the subject will be recorded using video camera and screen recording software, then to be analyzed by behavioral analysis tools so to eliminate possible bias to the result. Then, according to the revised data, draw a conclusion of the different window managing systems.
Undergraduates
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Expression and Isolation of Ligand Binding Domain of the GluR6 Subunit of the kainate Receptor

OLUWATIMILEHIN AJAYI

Southern Methodist University  Class of 2009

Sponsored by: Vasanthi Jayaraman, PhD, Department of Biochemistry and Molecular Biology

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

Key Words: AMPA, GluR6, Kainate and Ligand:protein

Glutamate receptors are the main receptors responsible for excitatory signaling in the central nervous system. They have been divided into three different subtypes based on their ligand binding affinities: AMPA, kainate, and NMDA. Crystal structures of the ligand binding core of all three subtypes have been determined and provided insight into the mechanism of action of these receptors, but what question still needs to be answered is how the specific interactions between the ligand and the protein lead to receptor function. Glutamate receptors are the main receptors responsible for excitatory signaling in the central nervous system. They have been divided into three different subtypes based on their ligand binding affinities: AMPA, kainate, and NMDA. Crystal structures of the ligand binding core of all three subtypes have been determined and provided insight into the mechanism of action of these receptors, but what question still needs to be answered is how the specific interactions between the ligand and the protein lead to receptor function.

While extensive studies have characterized the ligand:protein interactions in the AMPA subtype, there is very little information available about the kainate subtype. Our hypothesis is that while the two receptors exhibit different binding properties, the mechanism of activation is similar in these two proteins. To address this question the soluble domain of the kainate receptors needed to be expressed. In order to express this protein we introduced a histidine tag at the N-terminus of the ligand binding domain of the GluR6 subunit of the kainate receptor and expressed it in E. coli cells (Origami B E3 cells).

The His-tagged isolated ligand binding domain of GluR6 protein was separated using a Ni-NTA column and the His tag removed using thrombin digestion. The protein was then further purified using a SP-Sepharose column. This soluble ligand binding domain will then be further used for binding studies to characterize the ligand binding properties and also vibrational spectroscopic studies to look at the specific interactions between the ligand and the protein.
ABSTRACT

Cloning of CEL 1 Nuclease

STEPHANIE L. BARRETT

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Sponsored by:       Hope Northrup, MD, Department of Pediatrics, Division of Genetics
Supported by:       The University of Texas at Houston Medical School - Summer Research Program
Key Words:          Tuberous sclerosis complex, CEL 1 nuclease, cloning

Tuberous sclerosis complex is an autosomal dominant disease resulting in formation of tubers, benign neoplasms, most commonly found in the central nervous system. It is attributed to genetic mutation on chromosomes 9 and 16. Cases of mosaicism are the most difficult to detect due to varying degrees of mosaicism in a patient’s lymphocytes. The individual will have a combination of cells, some with the mutation and some without, and subsequently there are different amounts of the mutated allele available for detection. CEL 1 nuclease, isolated from celery, has demonstrated to be effective in detecting mutation by cleavage of DNA at sites of base-substitution mismatch. CEL 1 nuclease is not yet commercially available so we sought to clone and purify CEL 1 for later use in mutation detection. The pMALc2-CEL I and pMALp2-CEL I containing bacteria was grown in luria broth containing glucose and ampicillin. Once optical density at 600 nm reached 0.5, IPTG was added to the culture to induce CEL I expression. The cells were harvested then the pMALc2-CEL 1 cells were resuspended in column buffer and the pMALp2-CEL I cells were resuspended in tris/sucrose buffer. The maltose binding protein was purified by binding to amylose resin. The purification of the protein was tested with SDS-PAGE gel electrophoresis. The gel electrophoresis showed that further purification is needed.
ABSTRACT

A Randomized, Double-Blind Comparison of Dexmedetomidine and Remifentanil for Sedation During Awake Fiberoptic Intubation

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Sponsored by: Carin A. Hagberg, MD, Department of Anesthesiology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: difficult airway, awake fiberoptic, dexmedetomidine, remifentanil

Awake nasal or oral flexible fiberoptic intubation remains standard of care for difficult airway management. The success of this technique depends upon whether the patient is relaxed and cooperative, and able to maintain their airway with spontaneous ventilation. Remifentanil has been used in the past to achieve sufficient sedation, yet as a narcotic may cause respiratory depression. The purpose of this double-blind study was to determine if Dexmedetomidine (D), a centrally acting, selective alpha-2 agonist, is effective and safe during awake fiberoptic intubation, as compared to Remifentanil (R). Thirty patients with expected difficult airways were sedated with either Remifentanil or Dexmedetomidine for intubation. Three sets of pictures and words were given to each patient at different times in the perioperative period: before entering the operating room, upon induction, and following surgery. Hemodynamic parameters (heart rate and blood pressure), ventilatory parameters (respiratory rate and SpO2), bispectral index level, and Ramsay sedation level were recorded. Recall was assessed at 30 minute intervals for a period of 3 hours after surgery. All patients were successfully intubated with 71% percent of R cases intubated on the first attempt, as compared to 38% of the D cases. Minimal hemodynamic instability was observed in both groups; however, the incidence of O2 saturation<90% was greater in the R group. Intraoperative visual recall in D cases was significantly reduced (by 20%) and postoperative visual and verbal recall significantly improved (by 8.3% and 13.0%) as compared to R cases, suggesting that Dexmedetomidine is superior to Remifentanil for sedation during awake fiberoptic intubation.
ABSTRACT

Transplantation of human embryonic stem cell-derived alveolar epithelial type II cells

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Sponsored by: Rick A. Wetsel, PhD, Institute of Molecular Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: alveolar epithelial type II cells, human embryonic stem cells

Alveolar epithelial type II (ATII) cells play a critical role in distal lung injury repair by proliferating and differentiating into alveolar epithelial type I cells that cover ~95% of the alveolar surface. Accordingly many attempts have been made to direct embryonic stem (ES) cells towards ATII differentiation through means such as co-culture with pulmonary mesenchyme and selective media and growth factors; however, these procedures resulted in mixed cell populations of low purity. Recently Wang et al. (PNAS, 2007) described a technique generating pure populations of human ES cell-derived ATII (hES-ATII) cells through genetic selection for surfactant protein C (SPC) expressed uniquely in ATII cells. This summer the ability of hES-ATII cells to regenerate the lungs of scid mice damaged by bleomycin was examined. hES-ATII cells were prepared from H9 hES cells containing a SPC promoter-bleomycin resistance transgene by differentiating them on Matrigel-coated plates for eight days and then selecting for SPC expression by bleomycin treatment over four days. Following bleomycin-induced lung injury, hES-ATII cells were delivered via endotracheal intubation at days 0, 1, and 2. Nine days later the lungs were sectioned and H&E stained to reveal the extent of pulmonary fibrosis. Considerable interstitial thickening was seen in the bleomycin control, whereas the day 0 transplant showed significantly less fibrosis and the day 2 transplant appeared comparable to the saline control. Additionally the bleomycin control died prematurely on day 7 while the transplants persisted until lung extraction, further suggesting regenerative potential. These preliminary findings indicate that hES-ATII cells may be useful in the treatment of distal lung injury as seen in chronic obstructive pulmonary disease, asthma, and cystic fibrosis.
The Effect of Active Hexose Correlated Compound (AHCC) on the Skeletal System of Mice in the Hindlimb Unloading Model of Microgravity and Accelerated Aging

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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: AHCC, Aging, Spaceflight, Skeletal System, Bones, Mice, Hindlimb Unloading

Anti-Orthostatic Hindlimb Unloading (HU) is a ground-based model that causes adverse physiologic effects associated with spaceflight and aging, such as immune dysfunction and loss of bone properties. Active Hexose Correlated Compound (AHCC) is a polysaccharide extract, derived from Basidiomycetes (mushroom), which has been shown to enhance immune function. However, no previous study has examined its effects on the skeletal system. This study investigated the efficacy of AHCC on restoring properties of bone that are adversely affected by microgravity.

Eight ten week old Balb/c mice were in HU for one week with control and AHCC (0.4%) supplemented chow. Bones were removed for density determinations and structural analysis using Micro Computed Tomography (microCT) and Dual Energy X-ray Absorptiometry (DXA).

DXA analysis showed a decrease in bone mineral content (BMC) in the HU control group (Ci) compared to the non-HU control group (C) of 14.5% and 20.5% in the entire femur and distal femur, respectively. BMC is greater in the HU AHCC group (Ai) by 9.29% when compared to Ci. MicroCT analysis showed that Bone Mineral Density, Bone Volume%, Bone Surface to Bone Volume ratio, and Trabecular Number is lower in Ai compared to Ci; Trabecular Thickness and trabecular spacing (porosity) is greater in Ai.

Although supplementation with AHCC in microgravity conditions shows improvement in BMC, the other characteristics observed have slight similarities to osteoporotic bone. Further studies could evaluate the optimal dosage required, increase the weeks of suspensions and also increase the number of animals used.
ABSTRACT

Does Fortilin Interact with p53 in the Nucleus?

ANDREW CHIU Rice University Class of 2009

Sponsored by: Ken Fujise, MD, Division of Cardiology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Fortilin, p53, apoptosis

Background: Apoptosis regulation is critical in pathogenesis of a number of human diseases. Fortilin is an anti-apoptotic protein that regulates apoptosis and ensures cell survival. Fujise Lab has identified a specific interaction between fortilin and p53, a tumor suppressor protein. While fortilin has been found in both the nucleus and cytosol, it remains unknown where the fortilin-p53 interaction takes place within the cell.

Hypothesis: Here, we hypothesize that fortilin interacts with p53 in the nucleus.

Methodology: We performed immunocytochemical staining on HeLa cells—a cervical cancer cell line—with and without UV irradiation, using anti-fortilin and anti-p53 (DO-1) antibodies. Bound primary antibodies were visualized by secondary antibodies conjugated to Rhodamine Red-X and Alexa Fluor 488, respectively. The nucleus was stained with DRAQ-5. Leica TCS SP5 confocal microscopy was used to image the stained cells.

Results: In the absence of UV irradiation, there was weak p53 expression in the nucleus. Fortilin expression was also weak, diffusely distributed throughout the cell. Upon UV irradiation, p53 expression robustly increased. Overall fortilin expression was also increased. Strikingly, UV irradiation was associated with the redistribution of fortilin to the nucleus.

Conclusions: Under normal conditions, fortilin distributes diffusely throughout the cell. Upon UV irradiation and p53 induction in the nucleus, fortilin redistributes itself to the nucleus, allowing itself to interact with p53. It is possible that fortilin is a specific inhibitor of p53, capable of moving to the site of p53’s action, binding to and blocking the apoptotic activity of p53.
ABSTRACT

Determining Heteroplasm in MELAS

SAGAR P. CHOKSHI The University of Texas at Austin Class of 2008

Sponsored by: Mary Kay Koenig, MD, Department of Neurology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Mitochondrial genome, MELAS, heteroplasm

The mitochondrial genome has double stranded DNA with 16,569 base pairs. The genome is unique because it has a higher rate of mutation than nuclear DNA because it is more susceptible to oxidation. Also, each cell has up to hundreds of mitochondria with each mitochondrion having from 2-10 copies of circular DNA, thus equaling thousands of copies of mitochondrial DNA per cell. This allows many mutations to be present in a heteroplasmic state. Particularly, I studied a single point mutation (from A to G) at base pair 3243. This causes a defect in the tRNA that carries leucine in protein synthesis for the mitochondria, a disease known as MELAS. Because of the heteroplasmic nature of this DNA, the proportion of mutant mitochondria must meet a certain level to be considered symptomatic. Using two samples, one with mutant DNA and the other with wild type DNA, we conducted real time PCR assays to create a standard curve which could be used for future unknown samples. We can use this standard curve to determine the amount of mutation that would be symptomatic. Additionally, we will subject these cells to different conditions and then measure the ratio of mutant to wild-type DNA to determine if a shift to a more favorable profile occurs. This will allow us to determine how to shift the ratio in a clinical setting in order to make the mutation less prominent in patients with this particular disease.
ABSTRACT

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

BRANDON P. CHU  
Rhodes College  
Class of 2008

Sponsored by: Christine E. Koerner, MD, FAAP, FACEP, Chief, Division of Pediatric Emergency Medicine

Supported by: The University of Texas at Houston Medical School - Summer Research Program and UTHSC - Houston Department of Emergency Medicine

Key Words: Transillumination, pediatrics, venous access, emergency care, nursing, Veinlite

Transillumination is used to view veins by illuminating the skin. Veinlite is a transillumination device used to facilitate venous access. The purpose of this study is to determine whether Veinlite will assist venous access (reducing time and number of attempts), and lessen patient pain in comparison to standard of care. Additionally, the study will determine whether Veinlite can facilitate successful access in patients considered a “difficult” stick, and if Veinlite can be easily used by nurses with various cannulation experiences.

Patients 0-21 years requiring venous access will be recruited at an urban pediatric emergency medicine department. Verbal assent/consent will be obtained, and qualifying criteria (dark-skinned, dehydrated, overweight/obese, history of difficult vein access) will be noted prior to enrollment. A nurse, randomly assigned to Veinlite or standard of care, will be permitted a maximum of two venous access attempts. If unsuccessful, a second nurse will be permitted to use the same assigned method to continue the trial for up to two attempts. Data collection will end after (at most) 4 attempts. After venous access is successful, the nurse will assess patient pain via the Neonatal Infant Pain Scale (0-2 years), Wong-Baker FACES scale (3-7 years), or subjective 0-10 pain scale (8-21 years), and will note the amount of time cannulation took. The nurse will complete a questionnaire regarding her experience with cannulation and with Veinlite.

Results will be analyzed using the SPSS statistical package. We hypothesize that Veinlite will minimize patient pain and facilitate vein access for nurses of various backgrounds.
ABSTRACT

Development of a Regional Stroke Emergency Transport System

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Sponsored by: James C. Grotta, MD, Department of Neurology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: tPA, SETTRAC, stroke center

Purpose: Stroke is the third leading cause of death in America. The only approved acute stroke therapy, tPA, must be given within three hours of symptom onset. Most hospitals do not offer this therapy. The Texas Legislature enacted a bill that determined that each region in the state had to develop an emergency stroke transport plan to appropriately triage stroke patients. We developed a committee that designed and enacted a plan for the nine-county region comprising the SouthEast Texas Trauma Regional Advisory Council (SETTRAC).

Methods: After first identifying all of the fifty-one hospitals in SETTRAC, we wrote a letter to each hospital asking each to return a signed affidavit designating itself as either a level one, level two, or level three stroke center. We also identified and then notified each EMS agency in the region that they would be required to take all stroke patients seen within eight hours of symptom onset to the nearest stroke center. We located educational materials to use to in-service separately the hospitals and the EMS agencies as needed. Finally we created reporting forms for the EMS agencies and hospitals to use to track the destinations and treatment outcomes of stroke patients, and created a database and analysis plan.

Results: As of July 20, 2007, we have identified three level one, eight level two, and four level three stroke centers in SETTRAC and have notified all fifty-five EMS agencies to begin transporting acute stroke patients to these centers. We have arranged in-services for two of these centers. A plan for maintaining and enlarging this program has been developed.

Conclusion: It is feasible to develop and implement an emergency stroke transport system covering a large metropolitan and semi-rural region over a relatively short time.
ABSTRACT

Gene Expression Profiling of SP1 Pathways

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Sponsored by: Rong Yu, PhD, Department of Neurosurgery
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: SP1, microarray, gene expression

SP1 is a human transcription factor involved in gene expression; it has been shown to affect a range of biological processes from skeletal development to glucose metabolism. SP1 has been implicated in regulating angiogenesis and tumor development, and is thought to play a role in oxidative stress and aging. However, many of its functions and pathways have yet to be discovered or clarified. In order to get a clearer, more complete picture of the role of SP1, we performed a microarray on mRNA from HeLa cells in which the SP1 gene had been knocked down by siRNA transfection. We analyzed the results of the microarray by several bioinformatic programs. SP1 is thought to be a powerful activator in gene transcription, but we found that it may also serve as a suppressor of gene expression. Interestingly, when SP1 was knocked down, many genes involved in cell development, cell death, apoptosis, and inflammation were up-regulated. For example, the expression of BMF, which is known to cause cell death and apoptosis, was increased by almost 4 fold. Expression of ID1, a key controller/suppressor of cell differentiation and development, was up 2.5 fold. Other important genes including AGT, KRT8, and IL17D were up-regulated to a significant level. Overall, we saw that SP1 is a transcription factor that regulates the expression of many different genes. Our data here will serve as a starting point for more research into the specific genes or pathways controlled by SP1.
Impact Doctors Have on Patients Physical Activity

JORDAN GOODIE

Sam Houston State University
Class of 2007

Sponsored by: Phillip C. Johnson, M.D., Department of Internal Medicine General Division, Kevin O. Hwang, M.D., Department of Internal Medicine General Division

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

Key Words: physical activity

The purpose is to assess (1) feasibility of a primary care-community referral program for promoting physical activity and (2) impact of the program on physical activity. We describe methodology and baseline data for subjects enrolled to date.

The design is a randomized, controlled pilot study with target enrollment of 90 patients seen in the UT general medicine clinic. Eligibility criteria include age 18-65 years, nonpregnant, in contemplation or preparation stage of regular physical activity, and free of significant cardiovascular or pulmonary disease. Subjects are randomized to receive from the physician a physical activity prescription (prescription only) or a physical activity prescription plus referral to local YMCA facilities at a discounted membership rate and fitness professionals (prescription + referral). Assessments of community resource utilization, physical activity, and attitudes are at baseline and after 8 weeks. So far, 22% (50 of 224) of patients who completed the screening questionnaire have enrolled in the study. Average age of enrolled subjects is 45.8 ± 10.8 years and 70% are female. There is no significant difference in age or gender between enrolled and nonenrolled individuals.

Our results will inform the design of a larger randomized controlled trial to test the efficacy of a primary care-community referral program.
ABSTRACT

Development of screen for functional mutants of AtxA, a key regulator of virulence in Bacillus anthracis

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Sponsored by: Theresa M. Koehler, PhD, Department of Microbiology and Molecular Genetics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Molecular Basis of Infectious Diseases Training Grant T32 AI055449
Key Words: AtxA, screen, Bacillus anthracis

Bacillus anthracis is a Gram-positive bacterium and the causative agent of anthrax. The most important virulence factors produced by B. anthracis are toxin proteins and a capsule, whose genes are controlled by the key regulatory protein AtxA. Strains of B. anthracis that do not produce AtxA express very little toxin protein or capsule and are attenuated. The purpose of this project was to develop a method to determine which amino acids in AtxA are critical for its function. The project consists of two parts: construction of an AtxA-dependent promoter - green fluorescent protein (GFP) fusion to be used as a reporter of AtxA function, and creation of a randomly-mutated atxA library. The GFP reporter system was constructed by placing the GFP-encoding gene gfpmut3a under the control of the minimal functional promoter of a toxin gene (PpagA) regulated by AtxA. AtxA-dependent GFP expression and fluorescence were confirmed by microscopy. To generate a library of randomly-mutated copies of atxA, we utilized error-prone PCR (EP-PCR) and used deoxyinosine triphosphate (dITP) and limiting dNTP concentrations to promote base substitution mutations. The EP-PCR conditions were optimized to induce 1-4 random substitutions in each copy of atxA. The frequency and type of mutations were confirmed by sequencing. In the future, GFP expression in B. anthracis containing the GFP reporter system and a mutated copy of atxA may be measured quantitatively to correlate specific amino acid changes in AtxA with changes in AtxA function.
Genetic Screening and Identification of HPVs Affecting EV Patients.

MATTHEW B. HUANTE The Victoria College, Texas A&M Class of 2009

Sponsored by: Dr. Stephen K. Tyring MD, PhD, MBA; Department of Dermatology
Supported by: The Molecular Basis of Infectious Disease NIH training grant; The University of Texas at Houston Medical School - Summer Research Program
Key Words: Epidermodysplasia Verruciformis, EV, HPV, EVER1/TMC6, EVER2/TMC8

Epidermodysplasia Verruciformis (EV) is an autosomal recessive disease which results in susceptibility to Human Papillomaviruses (HPVs) of the Beta-PV (EV/HPV) genus. HPVs from this genus have been shown to increase the risk of skin cancer. EV has been linked to mutations in EVER1/TMC6 or EVER2/TMC8 novel genes on chromosome 17 (EV1 locus). These gene mutations have been found in 75% of EV patients. Specific genes on the second susceptibility locus, EV2, located on chromosome 2 have not yet been characterized.

This blinded study was designed to identify EV/HPV DNA in two brothers, with EV, utilizing the Polymerase Chain Reaction (PCR). The genetic studies could not link these EV cases to a mutation in the EVER genes implying that the genetic alteration must be occurring on the EV2 locus. A Nested PCR was used to amplify EV/HPV in DNA samples extracted from the patients' flat warts. Gel electrophoresis was then used to test for the presence of EV/HPV PCR fragments. The samples were labeled as putative positive if they produced a band within the size range of the HPV positive control DNA. Putative EV-HPV positive PCR products obtained from the patients were subjected to cloning and sequencing. The acquired sequencing data was used to identify HPV types by BLAST (Basic Local Alignment Search Tool) search and known HPV sequencing information deposited in the NCBI Gene Bank.

The first DNA sample, #72, showed the presence of HPV 38b subtype FA125 and HPV type 23. The second DNA sample, #92, showed the presence of HPV 38b subtype FA125 and HPV type 25. In conclusion both patients were infected with multiple EV/HPV types.
ABSTRACT

Immune Response to *Listeria monocytogenes*

**FARHEEN IBRAHIM**  
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Sponsored by: Rick Wetsel, PhD, Center for Immunology and Autoimmune Diseases  
Supported by: The University of Texas at Houston Medical School - Summer Research Program  
Key Words: infection, inflammation, *Listeria monocytogenes*

*Listeria monocytogenes*, contracted through ingestion of contaminated foods, is an intracellular gram-positive bacterium that causes septicaemia and meningitis in immunocompromised individuals and infection of the fetus in pregnant women. This bacterium has the ability to hijack the normal immune response to its advantage by destroying vital inflammatory responses needed to clear infection. C3a, a complement anaphylatoxin, mediates many proinflammatory activities on binding to its receptor, C3aR, which has also been implicated as a possible anti-inflammatory receptor. Because of its dual role in inflammation, we wanted to determine how C3aR functions in response to *L. monocytogenes* infection. C3aR-deficient mice and matched wild type (WT) C57BL/6 mice were inoculated intraperitoneally with *L. monocytogenes*. Higher bacterial counts in the spleens and livers of C3aR-deficient mice as opposed to their WT counterparts were observed two days after infection. C3aR-deficient mice also had higher levels of IL-1β and IL-6 in the spleen compared to the WT mice. In addition, lower levels of natural antibodies were observed in the serum of infected C3aR-deficient mice compared to infected WT mice, which could be attributed to the ability of *L. monocytogenes* to cause lymphocyte apoptosis. Despite higher levels of cytokines in the spleens compared to WT mice, C3aR-deficient mice still had greater bacterial counts, indicating that C3aR-deficient mice are more susceptible to *L. monocytogenes* infection and are unable to mount a proper immune response to counter infection.
ABSTRACT

HPV Typing and Confirming a Mutation of the TMC8/EVER2 Gene in an Epidermodysplasia Verruciformis Patient

LESLIE M. JEAN  University of Texas at Austin  Class of 2010

Sponsored by: Stephen K. Tyring, MD, PhD, MBA, Department of Dermatology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Department of Dermatology
Key Words: Epidermodysplasia Verruciformis, Human Papillomavirus, TMC8/EVER2 gene

Epidermodysplasia Verruciformis (EV) is a rare autosomal recessive genodermatosis characterized by flat warts and pityriasis versicolor lesions. EV has been linked to an unusual susceptibility to specific Human Papillomavirus (HPV) genotypes caused by mutation of the TMC6/EVER1 or TMC8/EVER2 genes. The objectives of the experiments were to determine which types of EV-HPV have infected an EV patient and to confirm that a homozygous c.1533G→T (p.K511N) mutation of the TMC8/EVER2 gene, detected by sequencing, exists in both the patient and his EV-affected brother. Our EV patient and his brother were born from consanguineous parents (first cousins). EV-HPV sequences in the patient were detected using nested PCR technology. For EV-HPV typing, the obtained putative EV-HPV sequences were cloned and sequenced by automated DNA sequencing, then compared to known sequences in an NCBI-GenBank database using BLAST search tool. Restriction fragment length polymorphism (RFLP) analysis was performed to determine whether the patient and his brother carry the same TMC8/EVER2 mutation. The BLAST search of the patient’s putative EV-HPV fragment sequencing data revealed high sequence similarities to the prototype sequences of EV-HPV -8 and -20. RFLP results showed that both the patient’s and his brother’s DNA were undigested by Mae I endonuclease and migrated the same distance in the agarose gel. The control DNA was digested by Mae I endonuclease. In conclusion, it has been confirmed that the patient is infected with EV-HPV types 8 and 20. It has also been confirmed that both brothers carry the c.1533G→T (p.K511N) TMC8/EVER2 homozygous mutation, based on evidence that they lost the same restriction site in their DNA.
ABSTRACT

Parvalbumin-Containing Amacrine Cells of the Monkey Retina

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Sponsored by:  David W. Marshak, PhD, Department of Neurobiology and Anatomy
Supported by:  The University of Texas at Houston Medical School - Summer Research Program, Grant EY06472 from the National Eye Institute
Key Words:  Calcium binding protein, Glycine, Primate, Rod pathway, Vision

The goal of this experiment was to describe the morphology and synaptic connections of amacrine cells in the primate retina containing the calcium binding protein parvalbumin (PV). Antibodies against parvalbumin (PV) were used to label retinas from 12 monkeys. Other markers included calbindin (CB), calretinin (CR), recoverin (RV) and choline acetyltransferase (ChAT). The results were analyzed using confocal microscopy. The PV-IR cells had an ovoid perikaryon and a single primary dendrite extending into the inner plexiform layer (IPL). The higher order dendrites were thin and wavy with large, spherical varicosities. The PV-IR amacrine cell resembles the knotty type 2 amacrine cell, also known as the A3 small-field amacrine cell, labeled using the Golgi method. The dendritic arbor of the PV-IR amacrine cell extends from approximately the middle of stratum 1 to the top of stratum 4 of the IPL. The PV-IR varicosities make numerous contacts with CR-IR AII amacrine cells at their lobular appendages. All amacrine cells receive input from other amacrine cells in stratum 2 but are not presynaptic to other amacrine cells there; therefore, we concluded that the PV-IR amacrine cell is presynaptic to the AII amacrine cell. The PV-IR amacrine cell varicosities have a centrally located indentation which may be occupied by RV-IR or by CB-IR bipolar cell axons. Therefore, the PV-IR amacrine cell interacts with both midget and diffuse bipolar cells. The PV-IR amacrine cell was positive for Glyt-1 and negative for GABA and therefore must use glycine as its neurotransmitter.
Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to have an injurious effect in the gastroenterological (GI) tract, where phospholipid membranes are part of a protective barrier. Certain NSAIDs (e.g. Indomethacin) are known to be secreted into the bile, which when combined with high concentrations of bile salts can potentially become even more toxic. To test this hypothesis, a series of biophysical experiments were performed. Changes in the octanol/water partition coefficient ($P_M$) of Indomethacin, a particularly toxic NSAID, was examined with or without bile salts, including cholate (CA), deoxycholate (DCA), glycocholate (GCA), taurocholate (TCA), and taurodeoxycholate (TDCA) using the classic Shake-Flask method (J Chromatogr A, 2004, 1037: 3-14). We found that deoxycholate (DCA) significantly lowered the $P_M$ of Indomethacin, suggesting interactions between the NSAID and DCA. The same trend was found when substituting cyclohexane as the organic phase in place of octanol. To further test the effect of Indomethacin with/without bile salts on phospholipid bilayer stability, the membrane dipole potential was examined. A voltage-sensitive fluorescent probe, di8-ANEPPS, was used to label the membrane composed of 90G (90% di-18:2 PC). The spectral shift of di8-ANEPPS is dependent on the dipole potential, which is correlated with lipid packing and membrane stability. It was found that increasing concentrations of DCA lowered the dipole potential in a dose-dependent manner and plateaued at ~ 6.5 mM. Addition of Indomethacin at both 0.5 mM and 2 mM shifted the dose curve downward, further suggesting that a combination of Indomethacin and DCA causes significant physical alterations to lipid membranes. This finding potentially explains the pathophysiological effect of NSAIDs, such as Indomethacin, in the bile.
ABSTRACT

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

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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

Calcium Movements In CGRP-Treated, Cultured, Skeletal Muscle Cells, Examined by Real-Time Spectroscopy and Deconvolution Microscopy: A Role for the Peptide in Tension Headache?

MICHELLE MANN Texas A&M University Class of 2008

Sponsored by: Roger J. Bick, PhD, Department of Pathology
Mya C. Schiess, MD, Department of Neurology

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

Key Words: Calcitonin Gene-Related Peptide, neuropeptides, myotubes, calcium, imaging

The role of calcitonin gene-related peptide (CGRP) has become a focus in research concerned with the unraveling pathways and mechanisms that contribute to severe headaches. Stress induced headaches affect many individuals causing not only much discomfort and high medical expense, but a major economical impact due to lost work hours. Previous research has reported high concentrations of CGRP in venous blood during migraine attacks, and data has been forthcoming to promote CGRP-blockers as potential therapeutic agents in treating severe headache but, apart from the role of CGRP in vasodilation, there has been little data supporting this. Previous findings in this lab with cardiomyocytes revealed that CGRP had a major influence on calcium fluxes and intracellular calcium levels. I therefore hypothesized that if CGRP caused increased calcium concentrations in skeletal muscle cells, then a continued, contractile state (tetanus) could develop and a severe headache might result. We employed a cell culture model, growing myoblasts into striated myotubes, then treating them with both a high (1µM) and a low (1nm) concentration of CGRP for a short (1 hr.) and a long (24 hr.) time period, then recording real-time fluorescent calcium fluctuations and constructing deconvoluted fluorescent images. When myotubes were incubated for one hour with a low dose of CGRP, large fluctuations in intracellular calcium levels were seen, with the striated myotubes exhibiting contractions. However, the high dose of neuropeptide resulted in calcium overload, a continuous contraction state and tetany. These results point to the possibility that CGRP has a potential major role in causing striated muscle-tension headaches as well as vaso-spasm migraine-type headaches. Our results were corroborated by myotubes showing a lack of calcium overload following exposure to the CGRP peptide 8-37. CGRP binding to cell surface receptors is thus a legitimate target for CGRP blockers in the treatment of tension headaches.
ABSTRACT

The Effects of Dendritic Cells On Mantle Cell Lymphoma Through Cocultures

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Sponsored by: Nami McCarty, PhD, Institute of Molecular Medicine Stem Cell Center
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Dendritic cells, cell surface markers, coculture

Some types of cancer are known to be upregulated by coculturing the cancer cell lines with dendritic cells. We believe that mantle cell lymphoma could also be upregulated by coculture, as well as would cause significant changes in cell surface markers. We did this by isolating monocytes from PBMC’s using CD14 microbeads and driving the monocytes to dendritic cells by culturing with GM-CSF and IL-4 for one week. We then used different concentrations of dendritic cells and cultured with both JEKO and SP53 mantle cell lymphoma cell lines. We then performed cell counts and FACS analysis for different cell surface markers. We compared these results to the cell counts and FACS analyses run before the coculture. We discovered that some of the cell surface markers change during the coculture. This leads us to believe that the dendritic cells have a direct effect on what surface antigens are expressed by the cell. We could not determine whether the cell lines had better clonogenicity after the coculture than they did before the coculture. We have concluded that mantle cell lymphoma cells are in fact affected by the dendritic cells and that through coculture the surface antigens will change. This could lead to significant advances in the way that cancer is treated. If certain cells are known to be in the cancer cycle with specific antigens that cell could be targeted and destroyed. We hope to soon find the progenitor (stem) cell of mantle cell lymphoma and identify its specific surface antigens.
ABSTRACT

Development of Interfering RNA Vectors to Reduce Scribble Protein Expression

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Sponsored by: Jeffrey A. Frost, PhD, Department of Integrative Biology & Pharmacology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: shRNA, APC, Dlg1, Scribble

Scribble, Lgl, and Dlg1 are tumor suppressor genes that act through a common signaling pathway. Mutations of these genes cause unrestricted cell proliferation in Drosophila and loss of polarity in mammalian cells. Furthermore, Dlg1 is a target for cancer causing oncogenes from DNA tumor viruses. Dlg1 is a scaffolding protein that coordinates the formation of signaling complexes. Although the molecular mechanism by which Dlg1 controls cell proliferation and polarity is unknown, it is presumed that the constituent proteins within these complexes determine the physiological effects of Dlg1.

To examine the importance of various proteins within Dlg1 signaling complexes, we have produced shRNA expressing vectors to downregulate the expression of Scribble and APC. Because the identification of effective shRNA target sequences is empirical, multiple constructs for both APC and Scribble were produced. Each vector was then tested for ability to reduce APC or Scribble expression in Hela and MCF7 cancer cells by Western blotting. None of the APC targeting vectors that were produced knocked down APC expression in either cell line. However, two of the three targeting vectors for Scribble were effective. These studies show that it is possible to target Scribble for RNAi-mediated degradation in MCF7 and Hela cancer cells.
ABSTRACT

All-Alpha Domain Function of Type IV Secretion System Coupling Proteins

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Sponsored by: Peter J. Christie, PhD, Department of Microbiology and Molecular Genetics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: All-Alpha Domain, T4S

Type IV secretion (T4S) systems are transmembrane multiprotein complexes that are important for the movement of protein and DNA between cells. One essential T4S subunit, termed the coupling protein, facilitates communication between DNA and protein substrates and the transport pore. In Agrobacterium tumefaciens, the causative agent of a tumorous disease in plants called Crown Gall, the VirD4 coupling protein mediates interactions between oncogenic DNA and effector proteins and a T4S system responsible for delivering these substrates to plant cells during the course of infection. In Enterococcus faecalis, a causative agent of gastrointestinal and cardiovascular infections in humans and other animals, the PcfC coupling protein facilitates docking of the tetracycline-resistance plasmid pCF10 with its cognate T4S system as a prerequisite to transfer to E. faecalis recipient cells. Based on an X-ray crystal structure of a VirD4/PcfC homolog, it has been proposed that an all-alpha domain (AAD) of this protein family interacts directly with substrate DNA and/or protein. Here, to test this hypothesis, I investigated the i) effect of exchanging the AAD’s of VirD4 and PcfC on substrate specificity, ii) producing mutant proteins deleted of their respective AAD’s, and iii) cloning each AAD for purification and subsequent in vitro substrate binding studies. Amplification of the sequence upstream and downstream of AAD was carried out. The 3’ downstream sections of pcfC and virD4 were inserted into PAP1, an expression vector. The 5’ upstream sections of pcfC and virD4 were inserted into the PGEM vector. Work is being done now to add the 5’ section into the PAP1 vector already containing the 3’ section. Insertion of the PcfC AAD between the virD4 5’ and 3’ sequence and visa versa will then be carried out. Future experiments will be conducted to study the interaction between the expressed AAD and other proteins such as relaxase, type IV secretion channel proteins and the interaction with DNA. This will hopefully show how proteins and DNA from bacteria are transferred to recipient cells.
ABSTRACT

Loss of Vancomycin Resistance in a Clinical Strain of *Enterococcus faecium*

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

Supported by: The University of Texas at Houston Medical School - Summer Research Program  
Molecular Basis of Infectious Diseases Training Grant (T32 AI055449)

Key Words: Enterococcus, vancomycin, antibiotic resistance, vanA

*Enterococcus faecium* is a common bacterium of the human gastrointestinal tract and can cause life threatening infections. The antibiotic vancomycin prevents normal cell wall synthesis in gram-positive bacteria by interfering with the normal processing of peptidoglycan precursors. Understanding the process of acquisition or loss of vancomycin-resistance genes would be useful in developing new therapeutic strategies. Two clonally related isolates of *E. faecium* were discovered in a patient with endocarditis and only one exhibited resistance to vancomycin. The objective of this study was to investigate if loss of vancomycin-resistance genes occurs *in vitro*. The resistant *E. faecium* strain was grown in brain-heart infusion (BHI) broth for six days in the absence of vancomycin. Subsequently, colonies were isolated on BHI agar and screened for the loss of the resistance phenotype in vancomycin-containing agar plates (64 μg/ml). A total of 284 colonies were screened resulting in one colony which did not grow on the antibiotic containing media (0.35% loss). Loss of the vancomycin-resistance genes was confirmed by a *vanA* PCR assay including appropriate controls. Single colony derivatives from the vancomycin-susceptible (VS) strain were obtained and typed by pulsed field gel electrophoresis (PFGE). The DNA was transferred to a nylon membrane and hybridization with a *vanA* probe was performed. The VS derivatives had identical PFGE pattern to that of the VR-*E. faecium*, and the *vanA* gene was not detected by hybridization, confirming loss of the resistance genes *in vitro*. Our results confirm the loss of vancomycin-resistance genes *in vitro* and suggest a similar phenomenon *in vivo*. 
ABSTRACT

Identification of AKAP18 and Adenylyl Cyclase Complexes

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

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

Key Words: Cyclic AMP, Adenylyl cyclase, A kinase anchoring proteins, PKA

The enzyme adenylyl cyclase plays a major role in signal transduction by converting ATP to cAMP, a second messenger that activates PKA, which in turn goes on to phosphorylate several intracellular targets. Specificity of signal transduction events are determined by a group of scaffolding proteins called A Kinase Anchoring Proteins. AKAPs contribute to specificity in signal transduction pathways and facilitate AC activation of PKA by forming signaling complexes that anchor PKA and other signaling molecules at specific subcellular locations. Previous studies revealed AC type V/VI is found in complexes with AKAP 79/150 and AC activity is associated with AKAP79/150. However, association of other members of the AKAP family with different isoforms of AC is not fully known. We set out to determine association, if any, of AKAP18 with AC isoforms III and V.

I made a GST-tagged AKAP18 construct and expressed it in E. coli BL21 cells. GST-tagged AKAP18 was purified using glutathione resin, resulting in a yield of 18.9 mg, from 4 liters of cells. Purified AKAP18 was used to pull down AC activity from rat heart and brain extract. Results showed GST-tagged AKAP18 pulled down higher AC activity than GST alone, indicating association of AC activity with AKAP18 in brain. In addition, FLAG-tagged AKAP18 was co-expressed in HEK293 cells with AC isoforms III and V. Flag-tagged AKAP18 was shown to express well in mammalian cells based on Western blotting for AKAP18, AC isoforms III & V, and PKA. Further studies will shed more insight into the specific associations and interactions of AKAP18 with different AC isoforms.
Characterizing Argonaute in the diploid fungus, *C. albicans*

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Sponsored by: Dr. Ambro van Hoof, PhD., Department of Microbiology and Molecular Genetics

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

Key Words: RNAi, Argonaute, *Candida albicans*, gene knockout, GFP

Small RNAs (20-24 nt) such as siRNAs and miRNAs play a variety of important roles in gene expression. All of these effects are mediated by a complex containing a protein of the argonaute family. Most eukaryotes have a functional RNAi pathway, and have both a dicer and an argonaute homolog. In fungi and plants, RNAi also requires an RNA dependent RNA polymerase (RDRP). Fungi, generally have all three proteins and a functional RNAi pathway (e.g. *Neurospora*), or lack all three protein and an RNAi pathway (e.g. *Saccharomyces*). In contrast, *Candida albicans* has an argonaute, but not a dicer or RDRP gene, and RNAi has not been reported in this fungus. This suggests that argonaute in *C. albicans* might have function that is independent of small RNAs, or that small RNAs are generated by a dicer independent mechanism. To study argonaute we attempted to knockout both copies of the gene in the diploid organism. All putative knockouts retained a wild type copy, probably through a duplication event, suggesting that Argonaute may have some essential function in this organism. Further attempts at gene knockout will use an inducible promoter that would allow the selective turn off of the gene. In some fungi, argonaute is a nuclear protein, and functions in heterochromatin formation, while in mammals Argonaute can be found in p-bodies. P-bodies are cytoplasmic sites of mRNA storage and degradation. We show that Argonaute-GFP in *C. albicans* localizes to cytoplasmic foci whose appearance resembles P-bodies, suggesting a function for *Candida* Argonaute in mRNA decay or translation repression. Argonaute protein has also been TAP tagged to isolate co-purifying RNAs and proteins. This initial analysis of *C. albicans* argonaute suggests that it may carry out an essential function in mRNA decay or translation repression. Further research should clarify this role, which may also be present in other species.
ABSTRACT

Nucleus Accumbens Lesions Modulate the Effects of MPD

ADAM PODET Tulane University Class of 2009

Sponsored by: Nachum Dafny, PHD, Department of Neurobiology and Anatomy
Alan C. Swann, MD, Department of Psychiatry

Supported by: The Pat Rutherford Chair in Psychiatry

Key Words: Methylphenidate, Nucleus Accumbens, Lesion, Sensitization

Psychostimulant medications such as Amph were used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children until it was discovered that Amph elicits dependency. The psychostimulant methylphenidate (MPD, Ritalin) has since become the drug of choice for treatment of ADHD. Repeated exposure to psychostimulants produces behavioral sensitization in rats, an experimental indicator of a drug’s potential liability. In studies on cocaine and amphetamine, this effect has been reported to involve the nucleus accumbens (NAc), one of the nuclei belonging to the motive circuit. The aim of this study was to investigate the role of the NAc on the expression of behavioral sensitization as a response to chronic MPD exposure. In the present study, 24 male Sprague-Dawley rats were divided randomly into three groups: an intact control group, a sham operated group, and a NAc bilateral lesion group. Locomotor activity was assessed for the first two hours following 2.5 mg/kg MPD injection, using an open field assay. Recordings were made before and after NAc lesions and during six days of continuous MPD administration, followed by three washout days and a re-challenge with the same dose (2.5 mg/kg) on the last day. Acute MPD exposure elicited an increase in locomotor activity in all three groups. However, the NAc lesion group exhibited a significantly higher increase in locomotor activity in comparison to sham and control groups. Chronic MPD did not elicit sensitization in the NAc lesion group, while both sham and control groups did exhibit increased locomotor activity (i.e., behavioral sensitization). These findings suggest that the NAc plays a significant role in the expression of sensitization due to chronic MPD exposure.
ABSTRACT

Rotavirus Infection Affects pP70s6k in the Rat Intestine

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Sponsored by: Dr. J. Marc Rhoads, M.D., Department of Pediatrics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Rotavirus; rat intestine; immunostaining

Rotavirus gastroenteritis affects children world-wide. Children will likely be infected before the age of 5 years but the peak of disease incidence occurs between the ages of 6 and 24 months. Children under the age of 2 years are most likely to become dehydrated and require admission. Therefore it is important to understand molecular mechanism involved in the disease.

Phosphorylation of P70S6k (pP70s6k) may regulate a much broader array of cellular responses, which together ultimately lead to transit of cells from G1 to S phase and thus of inducing cell growth. In order to investigate the level of pP70S6k during rotavirus infection, 5d old rat pups were infected with rhesus rotavirus. Immunostaining of the intestine showed downregulation of pP70s6k in the rotavirus infected intestine compared to the control rat intestine, as measured 2 days after infection. However by d4 of infection, the pP70s6k level returned to normal. Immunoreactivity for pP70s6k was most strong throughout the lamina propria and it was also present in all enterocytes along the crypt-villus axis. These studies suggest that pP70s6k is an important signal involved during rotavirus induced diarrhea in the rat model.

Acknowledgments: The author would like to thank Dr. Sankar Surendran and Ms. Sue Ellen Crawford for their valuable help in this project.
ABSTRACT

Genotyping of Known NAT2 Disease Alleles in NSCLP Population

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Sponsored by: Jacqueline T. Hecht, PhD, Department of Pediatrics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: NAT2, NSCLP, maternal smoking

Non-syndromic cleft lip with or without palate (NSCLP) is a common birth defect occurring in 1/700 livebirths and affecting 4000 newborns per year in the US. NSCLP is a complex disease involving multiple genes and environmental factors. Previous studies have shown that maternal smoking during pregnancy increases the risk of having an offspring with NSCLP. The N-acetyltransferase 2 (NAT2) gene is a biotransformation gene that metabolizes aromatic and heterocyclic amine carcinogens found in tobacco smoke. Variations in NAT2 can lead to a slower acetylation rate, increasing the amount of DNA adducts which have been associated with an increased risk for birth defects. We hypothesized that NAT2 polymorphic variants are associated with NSCLP. To test this hypothesis, polymorphic variants of NAT2 were genotyped in 130 multiplex families and 349 simplex Caucasian and Hispanic trios using TaqMan® assays. The data were analyzed using Family Based Association Testing (FBAT) and Haplotype Based Association Testing (HBAT). No association was found for NSCLP and NAT2 polymorphisms in this NSCLP dataset. These results suggest that variation in the NAT2 gene does not play a major role in the development of NSCLP.
Serotonin-induced Long-term Facilitation Causes Increased CREB1 Levels in Sensory Neurons of *Aplysia*

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Sponsored by:   John H. Byrne, PhD, Department of Neurobiology and Anatomy  
Supported by:   The University of Texas at Houston Medical School - Summer Research Program  
Key Words:   Transcription factor, CREB, memory consolidation, immunofluorescence

CAMP-response element binding protein (CREB) is a transcription factor that is believed to play a role in memory consolidation. In the marine mollusk *aplysia*, binding of the neurotransmitter serotonin (5-HT) to receptors on sensory neurons (SNs) leads to the phosphorylation of CREB1. Phosphorylation of CREB1 at Ser-85 and CREB1 binding to enhancer sequences termed CAMP-response elements (CREs), are required for activation of CREB1-mediated gene expression and appear necessary for the induction of long-term facilitation (LTF). CREB1 itself contains CREs in its promoter region, thus possessing the ability to induce its own gene transcription through a positive feedback mechanism. Previous results from Western blots indicate that 5-HT induces an increase in total CREB1 (tCREB1) which persists for at least 24 h following treatment in the pleural-pedal ganglia. The pleural-pedal ganglia consists of a multitude of neurons but SNs appear to be important in sensitization; 5-HT release facilitates sensory-to-motor synapses necessary for LTF. To verify these changes occur specifically in presynaptic SNs, we used immunofluorescence techniques coupled with confocal microscopy to measure changes of tCREB1 in cultured SNs at 24 h following 5-HT treatment. The immunoreactivity for tCREB1 is localized in both the cytoplasm and the nucleus. Consistent with Western blot results, tCREB1 levels are increased at 24 h post 5-HT treatment in SNs. Compared to control, 5-HT treatment induced a 22 ± 12% increase of tCREB1 immunoreactivity in the cell body (Mean ± SEM, 5-HT: 79.4 ± 14.6; Control: 64.5 ± 9.63) as well as a 26 ± 4% increase in the nucleus (5-HT: 81.1 ± 4.35; Control: 64.3 ± 1.25). These results indicate that changes in CREB1 protein measured with Western blot analysis of 5-HT treated ganglia are recapitulated in the SNs, suggesting that prolonged enhancement in CREB1 expression may be important for LTF consolidation.
Dysfunction of the dopamine (DA) system within the caudate-putamen (CPu), a component of the motor system that aids in the regulation of locomotor activities, is thought to be involved in Attention Deficit Hyperactive Disorder (ADHD). Abnormal DA levels within the CPu alter normal functioning and lead to symptomatic ADHD. Methylphenidate (MPD) therapy acts to restore normal DA levels and is the treatment of choice for ADHD. Continuous treatment with MPD can elicit behavioral sensitization, an experimental indicator of the drug’s potential to lead to dependency and addiction. The objective of this study was to assess whether the CPu is involved in the mechanism underlying MPD sensitization. Acute and chronic MPD was given to rats with selective lesions of the DA system within the CPu and an open field assay was used to record the locomotor activity. Three groups were used, 1) intact control, 2) sham lesion, and 3) selective neurochemical lesion of the DA system within the CPu. All groups received 2.5 mg/kg MPD injections for 6 days to induce behavioral sensitization, followed by 3 washout days and then a rechallenge of MPD. The data was evaluated in 4 phases: acute, induction, withdrawal, and expression. All three groups exhibited similar baseline activity and similar acute response to the initial MPD treatment. During the induction phase lesioned rats exhibited higher locomotor activity than intact rats immediately following MPD injection in 3 of 4 motor indices. Significant sensitization was observed in the expression phase of lesioned rats in only 2 of the 4 motor indices, compared to 3 of 4 indices in intact rats, with only one index in common. CPu lesions appear to increase and prolong the effect of chronic MPD on certain locomotive behaviors, indicating the role of the CPu, in part, in the induction and expression of MPD elicited behavioral sensitization.
Infant rhesus macaques (*Macaca mulatta*) require regular social interaction with age peers for proper emotional development. Insufficient social interaction during infancy of nursery reared animals results in the inability to cope with environmental stressors in adulthood and leads to a wide variety of maladaptive behaviors known collectively as “isolation syndrome” (Mason, 1968). While the monkeys do almost as well as their less isolated peers in some types of cognitive testing paradigms (Harlow *et al.*, 1969), their unpredictable behavior can result in aggressiveness towards caretakers or self injurious behavior (SIB). Maladaptive behavior in adults also results in the fear of novelty and a range of anti-social behaviors. This decreases the overall effectiveness of environmental enrichment programs based on social housing as these animals usually cannot be paired with conspecifics. Regular exposure to age matched peers in a surrogate – peer rearing paradigm during early development has been proven to prevent most of the symptoms of isolation syndrome (Hansen, 1966; Novak and Sackett, 2006). One to two week old infant macaques are received at the animal facility on a weekly basis. They are individually housed but can see and touch animals on either side. They are provided a surrogate plush toy as well as hanging towels and toys. They are bottle fed every 4 hours. The infant macaques are given between 10-30 minutes of group playtime, starting at ten minutes and increasing with age, three days a week. Groups begin as pairs expanding to quartets and larger groups as the infants grow older and more active. A pyramid stack of plastic crates and stuffed animals provide climbing surfaces and environmental enrichment during playtime. As there is no separation between the observer and the infants, the observer serves as an additional climbing surface. At one year of age, the infants are permanently pair or group housed. These programmatic changes have resulted in socially adapted juveniles and are expected to result in socially adapted adults as the animals mature.
ABSTRACT

Working Memory and Tourette Syndrome

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Sponsored by: Anne B. Sereno, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: working memory, eye movements, Tourette Syndrome

Research has found that individuals with Tourette Syndrome (TS) and Attention Deficit Hyperactivity Disorder (ADHD) exhibit differing impairments in executive functions such as attention and working memory (WM). A closer examination of WM in TS patients with and without comorbid ADHD could help distinguish these subtypes. The purpose of this study was to develop a reliable and robust measure of WM. Twelve normal adult participants were tested while their eye movements were recorded with an infrared eyetracker. For each trial, after participants fixated on a central point, a sequence of 3-4 targets appeared in 6 possible target locations evenly distributed around this fixation point. Within separate blocks of trials, participants were instructed to look to the location of either the last target (no WM condition) or second to last target (WM condition), with the final target in the sequence either remaining visible (to aid recall) or disappearing from the screen. Participants showed a WM effect, with significantly slower reaction times and significantly more errors in the WM condition versus the no WM condition. Furthermore, a greater WM effect (increased errors) occurred when the final target did not remain visible. Thus, this eye movement task proves to be an effective measure of WM, and removing the final target enhances the WM effect. The application of this task to TS patients with and without ADHD should provide a reliable and sensitive measure of WM. Differences in performance could aid in diagnosing subtypes and evaluating treatments for WM deficits.
ABSTRACT

HVM2 Mutations in Moyamoya Disease

CAROLYN SMITH-LIN Princeton University Class of 2010
Sponsored by: Dianna Milewicz, MD, PhD, Department of Medical Genetics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Moyamoya Disease, HVM2

Mutations in the HVM2 gene are a cause of familial thoracic aortic aneurysm disease and patent ductus arteriosus. Families with mutations in the HVM1 gene are also observed to have a significant family history of early onset strokes and other occlusive vascular diseases. Moyamoya disease is characterized by stenosis of the Circle of Willis leading to premature ischemic strokes. To compensate for the lack of perfusion, the brain creates smaller vessels to bypass the occluded main arteries. These smaller vessels or Moyamoya blood vessels increase blood flow in the brain but are more prone to rupture, also causing hemorrhagic strokes. Neurosurgical treatment to increase blood flow to the brain are highly successful in preventing strokes and therefore it is important to identify the factors that predispose individuals to this disease, including genetic factors. The genetic basis of Moyamoya disease has not been elucidated, and no genetic mutations have been identified in Moyamoya patients to date. We sequenced the HVM2 gene in DNA from 37 Moyamoya patients and identified one HVM2 mutation in this cohort, which is a recurrent mutation present in 3 patients with premature strokes. Functional studies addressing the pathways affected by HVM2 will aid in better diagnostic and possibly therapeutic approaches for Moyamoya disease.
ABSTRACT

Upregulation of Haptoglobin by Sulfarophane Provides Neuroprotection after Intracerebral Hemorrhage (ICH) in Rats

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Sponsored by: Jaroslaw Aronowski, PhD, Department of Neurology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: haptoglobin, intracerebral hemorrhage, sulfarophane, hemoglobin, oligodendrocytes

Following ICH, erythrocyte-derived hemoglobin (Hb) accumulates in the extracellular space and causes neuronal damage in ICH-affected brain. We had reported recently that activating transcription factor Nrf2 with Sulfarophane (SF; 5 mg/kg, ip. once a day for 7 days) could ameliorate neuronal death and the sensory-motor functional deficits in a mice ICH model, which was produced by intra-striatal injection of autologous blood. Here we found that this protective effect of SF is associated with the increased expression of an Hb-neutralizing protein, haptoglobin (Hp), in the hematoma-affected brain at 24h to 7d after initiation of treatment with SF. This SF-induced Hp increase was seen at both the mRNA and protein levels, as shown through RT-PCR and Western Blot, respectively. Immunohistochemistry studies demonstrated that Hp is mainly expressed in the oligodendrocytes in the hematoma-affected area, including the ipsilateral cortex, corpus callosum, sub-cortical nerve tract bundles. This SF-mediated Hp increase was associated with 30.5% acceleration in hematoma resolution, as established by the reduced Hb content in the hematoma-affected brains at 7 days after ICH.

Further, the in vitro study employing cultured primary mice neurons exposed to Hb with or without exogenous Hp indicated that Hp could reduce neuronal damage caused by Hb by 31.2% and 22.6%, as determined with LDH assay and neurofilament proteolysis, respectively, providing direct evidence that Hp is protective against the Hb-mediated neurotoxicity.

Thus, we postulate that upregulation of Hp in oligodendrocytes by SF may be an important mechanism in preventing Hb-mediated neurotoxicity and it could be developed into a potential therapeutic strategy for treatment of ICH.
ABSTRACT

Using the Counterselectable Marker, PheS, in the Genetic Analysis of *Borrelia burgdorferi*

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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: Phenylalanine, counterselectable markers, *Borrelia burgdorferi*

*Borrelia Burgdorferi* is a tick-transmitted spirochete that causes Lyme disease, an infection that can last months to years. *B. Burgdorferi’s* genetics are poorly understood, with few genetic tools available, and only recently a transformable strain was obtained. While this strain has low transformation efficiency as compare to other bacteria, the new strain allows us to open the field of Borrelia genetics. Counterselectable markers are genes that can be used as genetic tools for the selection of a specific recombination event yielding to the deletion of a targeted gene. Currently, there are no such markers available for Borrelia. In earlier studies, sacB, a commonly used counterselectable marker, have been found to not work well in Borrelia. An alternative will be to use *pheS* that encodes the α subunit of the Phe-tRNA synthetase. In *Escherichia coli*, a specific mutation *pheS294AG* confers relaxed substrate specificity, such that the mutant enzyme can aminoacylate tRNAPhe not only with phenylalanine but also with halogenated phenylalanine derivatives, including p-chloro-phenylalanine (p-Cl-Phe). Cultivation of *E. coli* clones expressing *pheS294AG* (*pheS*+) on medium with added p-Cl-Phe results in the inhibition of growth, presumably as a consequence of the production of non-functional proteins in which Phe residues have been replaced with p-Cl-Phe. We identified the Borrelia *pheS* homolog (BB0513), and by PCR-directed location, we introduced the mutation that confers *pheS* relaxed substrate specificity. We are finalizing the vector carrying the *pheS294AG* gene that will be introduced in Borrelia to test the putative utility of *pheS*+ as a counterselectable marker in Borrelia.
ABSTRACT

Cross-modal Validation of Diffusion Tensor Imaging and Cortico-Cortical Evoked Potentials

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Sponsored by: Nitin Tandon, MD, Department of Neurosurgery
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Cortico-cortical evoked potential, diffusion tensor imaging, subdural electrode

Implanted sub-dural electrodes (SDEs) are used to localize the onset of seizures in patients with refractory epilepsy. In addition to their usefulness in the clinical realm (ictal localization and cortical mapping), these electrodes provide a unique window for understanding brain function. Single pulse cortical stimulation using these electrodes elicits changes in local field potentials at remote locations, a phenomenon characterized as cortico-cortical evoked potentials (CCEPs). It is reasonable to assume that differences in white matter tracts connecting the stimulating and recording electrodes impact the propagation of CCEPs. Prior to surgical implantation of the SDEs, patients underwent a diffusion tensor imaging (DTI) sequence in a Philips 3T MR scanner. Following cortical stimulation mapping (CSM) for clinical purposes, electrodes where stimulation elicited dysnomia or dyslexia were stimulated in a bipolar fashion with balanced square wave 500-μsecond duration pulses delivered at 1Hz at low current strengths. Concurrent EEG recording was carried out at 1000Hz. Using the stimulus peak as reference, we averaged 50 CCEP epochs at each electrode pair. Post-operative CT images were used to co-register SDE locations with DTI tractography. In one left-lateralized language patient, we stimulated an electrode pair that evoked dysnomia in the left medial sub-temporal region and located the 20 largest amplitude CCEPs. Of the 16 electrodes remote to the stimulated grid, 12 contained direct fiber connections to the stimulating electrodes within a volume of interest (12mm x 12mm x 12mm). All of these fiber connections were consistent with the expected projections of the inferior longitudinal fasciculus. These results provide preliminary evidence that DTI and CCEPs can be used for cross-modal validation of connectivity assessments in the human brain.

Acknowledgements: Thanks to Timothy Ellmore, PhD, Department of Neurosurgery, and to Krishanthan Vigneswaran.
ABSTRACT

Oxaliplatin: Hematological Toxicity Dose Response in Rats

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Sponsored by:  Joan Bull, MD, Department of Internal Medicine
Supported by:  The University of Texas at Houston Medical School - Summer Research Program
Key Words:  Oxaliplatin, Leukocytes, Leukopenia, WBC differential,

Background:  Clinical evidence suggests that oxaliplatin induces hematological toxicity. This may inhibit treatment-induced anti-tumour immune response, recently observed in pre-clinical studies in this lab. There are no publications on hematological toxicity of oxaliplatin in rats. The purpose of this study was to measure leukopenia in non tumor-bearing F344 rats after injection of oxaliplatin.

Materials and Methods:  4 groups of 2 rats/group received the following doses of oxaliplatin by tail vein injection on day 0: 1) 14mg/kg, 2) 12mg/kg, 3) 10mg/kg, 4) 8 mg/kg. 14mg/kg is the maximally tolerated dose (MTD) in rats. A control rat received no treatment. Leukocytes were counted on days 0, 4, 7, and 10 by hemocytometer. Body weight (BW) was recorded and % BW loss computed on days 0, 4, 7, and 10.

WBC x 10^6 /ml blood dropped from a mean of 12.3, 9.0, 9.9, 9.4, on day 0 to a nadir of 3.4, 5.28, 4.70, 4.65, on days 7, 10, 7, 10 for groups 1-4 respectively. The control WBC remained between 10.0-13.4. (Percent BW drop for groups 1-4 respectively was 5%, 2.3%, 1%, 2% on day 2.

Conclusion:  Oxaliplatin induces dose-related hematological toxicity and BW loss compared to the control in rats. High doses and control group showed consistent blood count results, however, the intermediate and low dose yielded variability which may explain the immune related anti-tumour results we observe. A more complete study will be needed to assess the variability at the intermediate dose levels and the relationship of leukopenia and anti-tumour response.
ABSTRACT

TNF-α, IL-6 and IL-1β Expression in Spleens of Mice Injected with Mycobacterial Trehalose 6,6’-Dimycolate

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Sponsored by: Jeffrey K. Actor, Ph.D, Department of Pathology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: trehalose 6,6’-dimycolate, tuberculosis, cytokines, spleen

The role of trehalose 6,6’-dimycolate (TDM, cord factor) in virulence and pathogenesis of Mycobacterium tuberculosis infection within the lung has been amply studied, however, the effects of TDM challenge on other organs, such as the spleen, have not been extensively investigated.

Methods: The expression of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β in the spleen was determined post TDM injection. C57BL/6 mice were sacrificed on days 0, 1, 4, and 7 post challenge, and mRNA was extracted from the splenic tissue. The RNA underwent reverse transcription; resultant cDNA was amplified and analyzed by quantitative RT-PCR. Fold change in cytokine expression was reported relative to naïve controls.

Results: IL-6 expression remained steady, with a slight increase on day 1. TNF-α levels decreased by a factor of ten on day 1 and remained low through day 7, while IL-1β expression had decreased to a negligible amount on day 1 but increased ten-fold by day 4.

Summary: The appreciable decrease in TNF-α and IL-1β on day 1 suggests macrophages may exit the spleen to respond to the intrusion of TDM in the lung, leaving an initial deficit of the cytokine-producing phagocytes. Macrophage levels are subsequently restored as the inflammatory response in other organs matures, coinciding with response recovery in the spleen. These results may have further implications for the understanding of the systemic pathogenesis of M. tuberculosis infection, and the role of TDM in this process.
ABSTRACT

Assessment of Atherosclerosis In Different Mouse Strains With Or Without Gene Deficiency

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Sponsored by: Yong-Jian Geng, MD, PhD, Department of Internal Medicine(Cardiology)
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Atherosclerosis, Apolipoprotein

Background and Significance. Atherosclerosis is a chronic arterial disease with inflammation and lipid deposition in the vascular walls that can cause the arterial blood vessels to harden and restriction of blood flow. Atherosclerotic plaque rupture can trigger thrombosis which can form blood clots and cut off the circulation of blood to a given organ or tissue, such as heart and brain.

Hypothesis and Aims. I hypothesized that a mouse with deficiency in a lipid-regulating gene may have a greater risk for atherosclerosis over age. The aim was to determine whether atherosclerosis, in mice, was age-dependent.

Experimental Design. Three different strains at two different ages (3-4 months and 18-24 months) were studied, including Balb/c (Control), CD1-/-, and ApoE -/- mice. These mice were fed normal chow before sacrificing. The full aortic tissue was dissected, and connective tissue removed. After washed with phosphate buffered saline (PBS) and stained with Oil-Red O solution (0.1%) for 30 min. The stained aortas were observed and plaques defined with strong red color staining under a dissecting microscope and photographed.

Results. In eighteen mice examined in this experiment, the control mice showed little staining in their aortas but increased staining in 60% was found in aged aortic wall. ApoE-/- mice showed stronger staining. Three of the five old age control mice contained plaques on their aortas and two of the four old age experimental mice, while not even one of the younger aged mice, control or experimental, contained any plaques on their aortas. In conclusion, atherosclerosis is a disease that is definitely dependent on old age.
fMRI Analysis of Naming Tasks Using Block Design and Event Related Paradigms

KRISHANTHAN VIGNESWARAN Vanderbilt University Class of 2008

Sponsored by: Nitin Tandon, MD, Assistant Professor, Department of Neurosurgery
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: fMRI, language, block design, event related,

During temporal lobe resections for treatment of epilepsy and brain tumors, neurosurgeons have to preserve language function. Pre-operative fMRI scans help localize regions involved in various cognitive processes. Instead of a traditional block design, we used rapid presentation event related (RPER) design in an fMRI study of naming. In a block design, stimuli are organized in categories and presented individually in runs consisting of ‘on’ blocks with images, and ‘off’ blocks with scrambled images. RPER designs have a variety of stimuli presented in a non-categorized random order, with ‘null’ stimuli presented during the run. RPER designs provide sequences that are resistant to habituation and expectation and can generate data to study cortical activation generated by categorized subtypes of stimuli and to determine behavioral responses based on naming latency.

Function MR(fMRI) data were obtained in a 3T scanner using Blood Oxygen Level Dependent (BOLD) imaging with a repletion time(TR) of 2015ms. Grayscale images of common objects (collected from the Boston Naming Test), famous faces, and their scrambled counterparts. RPER stimuli were ordered using optseq2, a stimuli scheduling optimization tool. Patients pressed a button and silently named equal numbers of stimuli over four RPER runs and two block design famous face and common object runs. Data were analyzed using Analysis of Functional NeuroImaging (AFNI) software.

Both RPER and block design paradigms show Broca’s area (speech production BA 44,45) activation. However, analysis of RPER data using AFNI shows differences in signal strength with activity in RPER experiments at a higher threshold with a p<4.7e-9 that cannot be detected in block design experiments. Further analysis would involve comparing famous face activation against common object activation in RPER, and using reaction times, measured using a button press response, as regressors for behavioral studies categorized by differences in response latency.

Acknowledgements: Dr Timothy Ellmore, Bryan Stierman
ABSTRACT

HVM2 Mutations Present in Stroke and Myocardial Infarction Patients

CARLOS A. VILLAMIZAR College of St. Scholastica Class of 2009

Sponsored by: Dianna Milewicz, MD, PhD, Department of Medical Genetics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: stroke, myocardial Infarction, genetic predisposition

Stroke is a cardiovascular disease that occurs when a blood vessel in the brain is either occluded or ruptured, causing hypoxia and eventual death of the cells. Similarly, myocardial infarctions (MI) occur when low blood flow due to a blockage in one of the coronary arteries, similarly leading to hypoxia. Mutations in HVM2 have been previously linked to individuals with familial thoracic aortic aneurysms and dissections (FTAAD) and patent ductus arteriosis (PDA). While studying these patient's families we also found history of premature stroke and MI. Furthermore, HVM2 mutations were observed to result in SMC disarray in the aortic media, weakening the vessel walls. Additionally, SMC hyperplasia was observed in the aortic media as well as in smaller vessels of the vasa vasorum, resulting in narrowing or occlusion of these vessels. This led us to believe that mutations in HVM2 could also be the cause of occlusive vascular diseases such as stroke and MI. On sequencing and analyzing HVM2 in 356 stroke and MI patients, we identified 9 patients with non synonymous coding mutations not present ethnically matched controls. These results confirm that HVM2 mutations predispose to a wide spectrum of vascular disease, including strokes and MI. Future studies will determine the functional consequences of HVM2 mutations as well as the mechanisms leading to the various diseases.
ABSTRACT

Observational Study of Silicone Reactions Among Burn Patients

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Sponsored by: David J. Wainwright, MD, Department of Surgery—Division of Plastic and Reconstructive Surgery

Supported by: David J. Wainwright, M.D., Department of Surgery
The University of Texas at Houston Medical School – Summer Research Program

Key Words: Silicone reaction, hypertrophic scar, burn

Silicone is a topical treatment commonly used in the scar management of hypertrophic scars and keloids caused by thermal and traumatic injuries. Although silicone gel sheeting may aesthetically improve the appearance of scars, potential side effects such as pruritis, rash, and other symptoms can arise causing great discomfort to the patient.

Purpose: This retrospective study served as an observational evaluation of the silicone related reactions among burn victims.

Methodology: An intensive chart review of 70 burn patients that were prescribed silicone was preformed and the data pool was narrowed to 25 patients and further segregated into a non-reaction control and reaction group. To facilitate further analysis, a database was created, which included details on the patient demographics, the burn injury, silicone, and treatment before and after the reaction. Reaction patients were analyzed singularly and then compared to the non-reaction patients.

Results: 11 patients were identified that developed skin reactions, 5 males and 6 females. 9% of these people were African American, 9% were Hispanic, and 82% were Caucasian. The average age of patients with reactions was 38 years old. These 11 patients were noted as forming reactions because of their development of persistent pruritis, rashes, pustules, and skin breakdown. Most of the skin reactions occurred in the upper extremities and appeared, on average 17 days after the initiation of the silicone gel sheets. Skin reaction seemed more common in fair-skinned people.

Conclusion: Based on this small sample population, the incidence of silicone related skin reactions would appear to be at least 16%. Additionally, a possible negative correlation between skin type and incidence of reaction was noted. This study was a preliminary evaluation on a future, extensive evaluation of silicone related skin reactions.
Identification of Insertion Sites of *Borrelia burgdorferi* STM mutants by *E. coli* Rescue

**BRITTANY K. WISE** Rice University Class of 2010

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: Lyme disease, Borrelia burgdorferi, signature-tagged mutagenesis

Lyme disease is the most prevalent tick-borne infection in the United States. *Borrelia burgdorferi* is the causative agent of Lyme disease and is transmitted by ticks. In order to identify the virulence factors required for infection, signature-tagged mutagenesis in a transformable, infectious clone of *B. burgdorferi* B31 were constructed to analyze the roles of the genes in the infection. The insertion sites of STM clones can be determined by inverse PCR or *E. coli* rescue methods. Basically, the signature-tagged pMarGentKan vector is introduced to the *B. burgdorferi* organism by electroporation and then inserted into a single gene in genome. The genomic DNA is isolated and digested with *Hind*III enzyme. The fragments are self-ligated with T4 ligase and the plasmid DNA is rescued in *E. coli*. Another alternative method is inverse PCR in which inverse polymerase chain reaction (PCR) is carried out by using ligation reactions. The rescued plasmid DNA and cleaned PCR products were used for gene sequencing. Analysis of the gene sequences will be performed using BLAST (Basic Local Alignment Search Tool) and the insertion sites of the STM mutants are identified. To date, significant progress has been made. From Tag 8, 10, and 11 mutants, 163 out of 182 cultures have rescued plasmid DNA or PCR product. Future work will include continuation of preparing plasmid DNA for gene sequencing in all 12 tags, and then later determining the insertion sites of these STM mutants so that infectivity of STM mutants can be detected in mice and ticks.
ABSTRACT

Activation of AMP Kinase Increases mRNA Transcript Levels of the Ubiquitin Ligases Mafbx/Atrogin-1 and MuRF-1 in Cardiomyocytes

JENNY ZHOU Emory University Class of 2009
Sponsored by: Heinrich Taegtmeyer, MD, DPhil, Dept of Internal Medicine- Cardiology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Ubiquitin ligases, AMP Kinase, protein degradation

Background: In patients left ventricular hypertrophy increases death and disability from heart failure. Conventional strategies used to reverse cardiac hypertrophy focus on decreasing pro-hypertrophic signaling. However, this approach has been unsuccessful because of the enormous redundancy within the pro-hypertrophic signaling network. Because hypertrophy and atrophy result from changes in the ratio of protein synthesis to protein degradation, we are proposing a new approach to reverse cardiac hypertrophy via the activation of pro-atrophic signaling pathways. Previous studies in skeletal muscle have shown that activation of the two ubiquitin ligases, Muscle atrophy F-box protein (Mafbx/Atrogin-1) and Muscle Ring Finger 1 (MuRF-1), increase protein degradation in vivo and in vitro.

Hypothesis: Activation of AMP kinase reverses cardiac hypertrophy through induction of Mafbx/Atrogin 1 and MuRF-1 in neonatal rat ventricular myocytes (NRVM).

Methods: In vitro, NRVM were treated with a pharmacological activator of AMPK, Metformin (1,1-dimethyl biguanide HCl). In vivo, Mice were injected with Metformin (250mg/kg by IP injection) for five days. Myocytes from both experiments were then lysed and harvested. RNA was isolated and subjected to quantitative RT-PCR.

Results: Metformin increases transcript levels of Mafbx/Atrogin 1 and MuRF-1 in vitro. However, five days of Metformin treatment was not sufficient to increase transcript levels of Mafbx/Atrogin 1 and MuRF-1 in vivo.

Future Experiments: Branched chain amino acids are known to increase protein synthesis, but their effect on protein degradation is not known. We will investigate whether different groups of amino acids affect the expression of Mafbx and MuRF-1, which may lead to the discovery of a novel regulatory pathway of protein degradation.
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FOOTNOTE

Jimmie Pope served as the coordinator for the program from 2001 – when the program was moved from Dr. Gil Castro at UCT - until her retirement in February 2008.

“I have been fortunate to work with such a wonderful program and the students who pass through it -- to, hopefully, careers in some area of research. The opportunity to witness the students enthusiasm for research and, especially, the faculty mentors efforts to insure that the students get the best possible experience has been gratifying. I am proud of the way we took the small program, and enlarged student participation and expanded into new areas. The new international section has been a challenge to get started but very rewarding. It is with heavy heart that I leave the program.”

The new coordinator will be Linda Guardiola.
2007 Summer Research Program Medical Student Participants
2007 Summer Research Program Undergraduate Participants