2006

Summer Research Program

Student Abstracts

The University of Texas
Health Science Center at Houston

Contents

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 1,500 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 second 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

Acknowledgements

This publication marks the completion of the twenty-first year of The University of Texas-at Houston Medical School (UTHMS) 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 Jerry Wolinsky, M.D., Dean, 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.

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 new international initiative now 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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Medical Students

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ABSTRACT

A Single Nucleotide Polymorphism in the Human Secretor (FUT-2) Gene Increases Susceptibility to Travelers' Diarrhea in Caucasian US Travelers to Mexico

STEPHANIE ADRIANSE University of Texas at Houston Medical School Class of 2009

Sponsored by: Pablo C. Okhuysen, MD, Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Travelers' diarrhea, FUT-2, single nucleotide polymorphism

Travelers' diarrhea (TD) affects 40-60% of US travelers to Mexico and is mostly due to bacterial enteric pathogens. Fucosylated proteins on the surface of the intestinal epithelium can function as receptors for enteric pathogens and determine the secretor status of an individual. The purpose of this study was to investigate if subjects with single nucleotide polymorphisms (SNP) in the fucosyltransferase gene (*FUT-2)* were associated with susceptibility to TD. The relative frequencies of four distinct SNPS in *FUT-2* were studied in a group of US travelers to Mexico. Subjects with TD provided a stool for microbiology studies. Only one of the four SNPs (rs10415215), which codes for a transition of A→G, demonstrated an association with TD and was therefore selected for further analysis. Among the 471 Caucasian travelers studied, 220 (47%) developed TD. Subjects with the non AA genotype were more likely to experience TD (27 of 40 or 67.5%) when compared to those that were of the AA genotype (193 of 431 or 44.8%) p=.005 resulting in a RR of 1.7 (95% CI of 1.078-2.677). The association remained significant for diarrhea due to all bacterial pathogens p=0.001 RR 1.5 (95% CI 1.055-2.332) as well as diarrhea due to Enterotoxigenic *E. coli* p=0.007 RR 1.42 (95% CI 1.015-1.997). This study provides evidence that Caucasian travelers with the non AA genotype at the *FUT-2* rs10415215 are more susceptible to TD when visiting Mexico.

ABSTRACT

Effect of COX Inhibition on Rat Gastric Matrix Metalloproteinase Production During Endotoxemia

CLINT R. BEICKER The University of Texas at Houston Medical School Class of 2009

Sponsored by: Emily K. Robinson, M.D., Department of Surgery
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Matrix Metalloproteinase, COX inhibition, SC560, NS398

Introduction: Prior studies in our laboratory have demonstrated increased matrix metalloproteinase production, specifically MMP-2, in the stomach following LPS administration which was associated with increased iNOS protein production. LPS increases COX-2 production in the stomach and may affect MMP activity. Studies in breast cancer cell lines have demonstrated increased COX-2 expression associated with increased MMP-2 activity. Additionally, COX-1 plays an important role in gastric mucosal defense but whether it has any influence on MMPs is unknown. We hypothesized that changes in COX function would modulate MMP levels; therefore we evaluated the effect of selective COX-1 and COX-2 inhibition on LPS mediated MMP-2 production.
Methods: Rats were given vehicle (DMSO) or the selective COX-2 inhibitor NS398 (3mg/kg IP), or the selective COX-1 inhibitor SC560 (40mg/kg IP) one hour prior to the administration of LPS (20mg/kg IP) whereas control animals received saline. The animals were sacrificed 24 hours after LPS administration and gastric mucosa was harvested. Gastric luminal fluid accumulation was measured along with gastric pH. MMP-2, MT-1 MMP, and iNOS production were assessed using Western immunoblot.
Results: LPS significantly increased gastric MMP-2, iNOS, and MT-1 MMP protein production while significantly increasing gastric volume and luminal fluid pH. SC560 significantly reduced LPS-induced MT-1 MMP and iNOS production while attenuating the increase in MMP-2, gastric volume and pH when compared to vehicle (DMSO). NS398 significantly reduced LPS-induced iNOS protein production but had no affect on MMP-2, MT-1 MMP, or gastric luminal fluid volume and pH.
Conclusion: LPS-induced MMP-2 production in the gastric lumen is COX-1, not COX-2 dependent.

ABSTRACT

Changes in Renal Phosphate Handling in X-Linked Hypophosphatemic Rickets

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Sponsored by: Mary D. Ruppe, MD, Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: XLH, FGF-23, MEPE

X-linked hypophosphatemic rickets (XLH) is the most common form of inherited renal phosphate wasting, affecting 1 in 20,000 children. Characterized by low serum phosphate, inappropriate 1,25 dihydroxyvitamin D levels and low renal tubular resorption of phosphate (TRP), patients experience bone pain, short stature, lower extremity deformities and dental abscesses. Novel regulators of phosphate, including fibroblast growth factor-23 (FGF-23) and matrix extracellular phosphoglycoprotein (MEPE), are implicated in the pathogenesis of XLH. Current treatment of oral phosphate and calcitriol (1,25 dihydroxyvitamin D3), improves symptoms but does not normalize height. We hypothesized that as long bone development was completed medication requirements would diminish. A relational database was developed to evaluate clinical parameters from a cohort of 100 XLH patients from the Shriner's Hospital. Techniques for extracting RNA from affected tissues, such as teeth and bone, were developed to study key gene expression. Steps to establish an assay measuring serum levels of FGF-23 were initiated. Analysis revealed that throughout childhood TRP is below normal, but in early adolescence begins to increase to near normal. Paralleling this increase, oral phosphate requirements decrease while calcitriol requirements are unchanged. These changes occur prior to completion of long bone growth, suggesting that factors other than treatment variables contribute to peak height attainment. Further exploration of essential genes and proteins implicated in the development of XLH will improve our understanding of the pathophysiology. Work done during the summer research program is the first step in the development of novel therapies to improve height attainment in X-linked hypophosphatemic rickets.

ABSTRACT

The Complications of Using Calcium Phosphate Cement in Craniofacial Reconstructive Surgery

CHRIS M. CASSARA The University of Texas at Houston Medical School Class of 2009

Sponsored by: John F. Teichgraeber, MD, Department of Surgery /Pediatric
Supported by: John F. Teichgraeber, MD, Department of Surgery/Pediatric
Key Words: Hydroxyapatite, HA, craniofacial, maxillofacial, bone substitute

A number of bone substitutes have been introduced over the last 5 years for use in reconstruction of the facial skeleton (i.e. Bone Source®, Mimic®, Norian CRS®). Little has been written on the complications encountered with clinical use of these materials. The purpose of this study is to present the experience with complications using bone substitutes in a variety of clinical settings, including reconstruction of post-traumatic defects and craniofacial deformities.

A retrospective study was carried out to include all patients that had undergone maxillofacial or craniofacial procedures involving Bone Source®, Mimic®, and Norian CRS® at the affiliate hospitals of The University of Texas Health Science Center at Houston. A total of 21 patients were treated with bone substitute materials between January 1998 and December 2005. The patient population comprised 9 females and 12 males, and the median age of the patients was 10.5 years. In this group of patients, the bone substitutes were used in children for recontouring and augmentation of the cranial vault or reconstruction of the frontal sinus and zygomatico-orbital complex. Complications were seen in 8 patients, of which 3 were minor and resolved with conservative therapy (antibiotics). However 5 required surgical debridement. The clinical picture seen in each case was fluid collection with mild erythema at the site of implant placement. In one patient, significant soft tissue infection was noted. This patient had a post-op incidental facial infection that colonized the cranial vault reconstruction. All 5 patients that required secondary surgery had evidence of loose bone substitute material on CT scan. Pathologic diagnosis in all cases was chronic inflammation. The authors found conservative therapy to be effective in patients who showed no evidence of loose bone substitute material on CT scan.

ABSTRACT

Employment Outcomes in Liver Transplant Patients

MARQUITA R. DECKER The University of Texas at Houston Medical School Class of 2009

Sponsored by: S. Chris Pappas, MD, Department of Internal Medicine/Gastroenterology, Hepatology & Nutrition

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14

Key Words: Liver Transplant, Outcomes, Employment

Sixty to seventy percent of patients who have received a liver transplant and do well medically do not become employed following recovery from this procedure. An IRB approved study was designed to determine 1) why many healthy patients do not re-enter the workforce 2) whether or not employment status is influenced by patients' access to health insurance or disability benefits 3) whether or not access to healthcare coverage is a stronger determinant of employment outcome than actual health status. An employment questionnaire for liver transplant recipients was designed specifically to address these questions for this study. A group of 118 patients from a database of Texas Liver Center transplant recipients will be sent an English and a Spanish version of the questionnaire. Structured interviews will take place with up to 10 patients from the same database to obtain descriptive answers to the questionnaire. After questionnaires have been collected and interviews are complete, analysis will involve: *measuring the proportion of employed to unemployed healthy patients *comparing unemployed patients to employed patients that have the same or similar health status *reporting the percentages of responses to the given multiple choice questions that address employment status and healthcare coverage. This study is significant in that it is the first to specifically describe employment status post-transplantation as it relates to healthcare coverage. This study has initiated necessary investigation of a healthcare outcome and facilitated future study and policy analysis of social security benefits and other support systems for liver transplant recipients.

ABSTRACT

Evaluating Candidate Genes for Cornelia de Lange Syndrome

EDWARD J. ESPINELI The University of Texas at Houston Medical School Class of 2009

Sponsored by: Kit-Sing Au, Ph.D. and Hope Northrup, MD, Department of Pediatrics/Genetics
Supported by: Kit-Sing Au, Ph.D. and Hope Northrup, MD, Department of Pediatrics/Genetics
Key Words: CdLS, NIPBL, SMC1L1, chromosome 10p13

Cornelia de Lange Syndrome (CdLS) is a multiple congenital anomaly disorder that commonly produces cognitive, facial, cardiac, ophthalmologic, genitourinary, gastroesophageal, and limb abnormalities. This dominantly inherited syndrome has been estimated to afflict up to 1 in 10,000, and recently, progress was made in identifying two disease-causing genes. One gene, *NIPBL* (after its homology to the *Nipped B* gene of *Drosophila melanogaster*) is known to associate with 47% of CdLS cases, and the other gene (SMC1L1) is associated with x-linked CdLS. However, approximately 53% of cases are still unaccounted for after the two known genes were screened. Through fluorescence in-situ hybridization study of a CdLS patient with chromosome translocation (10p13:16p13), we identified two genes on 10p13 as possible candidate genes for these non-*NIPBL* cases. The purpose of this project is to investigate whether mutations in these other candidate genes do indeed cause CdLS. First, we amplified and sequenced the known mutation bearing exons of NIPBL and SMC1L1 to identify patients with mutations in these two known disease causing genes. Then, the patients with no mutation identified on NIPBL or SMC1L1 were subjected to screening for mutation on the exons of the two 10p13 candidate genes. Current analysis shows several variants in these genes in several CdLS patients. We are currently examining the parental DNAs and controls to verify the significance of these variants.

ABSTRACT

Second Place Winner, 2006 Frank Webber Prize for Student Research

Orthopaedic Complications in Diabetic College Athletes: A Retrospective Analysis

KENNETH ESTRERA The University of Texas at Houston Medical School Class of 2009

Sponsored by: Thomas O. Clanton, MD, Department of Orthopaedic Surgery
Catherine G. Ambrose, PhD, Department of Orthopaedic Surgery

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14

Key Words: Diabetes, college, athletics, NCAA, orthopaedic,

Background: College athletes with diabetes mellitus may find that an intense exercise regimen may have healthy benefits in regard to their disease, but they may also be introduced to a number of potential risks at the same time. Along with metabolic problems, athletes may become susceptible to a number of orthopaedic problems as a result of diabetes related neuropathy, vascular disease, or a decrease in bone mass. We described and analyzed the effect of diabetic orthopaedic complications on college athletes.

Materials and Methods: An IRB approved retrospective study was designed to determine the prevalence of diabetes in NCAA athletics, determine the incidence of various injuries and complications that may be related to diabetes, and compare incidence of these injuries between a population of diabetic and non-diabetic athletes. A survey requesting information on diabetic athletes was distributed to athletic trainers at 887 NCAA athletic programs at the division I, II, and III level.

Results: To date, 98 schools have responded representing 36,861 college athletes with 43 of these athletes having been diagnosed with diabetes. Within this group of diabetic athletes, 53.49% of them reported problems that included hyperglycemic or hypoglycemic episodes, fractures, foot problems, delayed injury healing, serious infections, and hospital or ER visits as a result of these problems. These statistics on diabetic athletes were compared with an established database of college athletic injuries compiled by the NCAA Injury Surveillance System (Need reference) in order to provide insight on the injuries that are more prevalent among diabetic athletes competing at the college level.

Conclusions: With a better understanding of diabetes in the NCAA athletic setting, trainers and team physicians will be better prepared to manage this disease and provide more effective care for the diabetic athlete.

ABSTRACT

A Single Nucleotide Polymorphism (SNP) in the Exon15 Region of the Lactoferrin Gene (LTFEx15) is Associated With Travelers' Diarrhea (TD)

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Sponsored by: Pablo C. Okhuysen, MD, Diepartment of Internal Medicine/Infectious Diseases
Supported by: NIH DMID grant R01 AI054948-05
Key Words: Lactoferrin, Travelers Diarrhea, SNP

Lactoferrin, an antibacterial iron-binding glycoprotein, is released from secondary granules of neutrophils in response to inflammation. Elevated levels of fecal lactoferrin (FL) can occur during bacterial diarrhea. In this study, we investigated the association of a SNP with susceptibility to TD and FL levels. Genotyping was performed in several SNPs of the LFR gene region by PCR followed by pyrosequencing in DNA extracted from US travelers with and without diarrhea during short-term stays in Mexico. A SNP LTFEx15 (T→C) (rs9110) was significantly associated with TD and thus was selected for genotype-phenotype correlations with fecal LF as determined by ELISA. Among 406 subjects, the frequency of the LTFEx15 T→C substitution for each genotype was 9% for CC, 42% for TC, and 49% for TT. The frequency for the C and T allele was 36.2% and 63.8% for healthy controls versus 24.9% and 75.1% for diarrhea cases respectively (P = 0.0005; RR 1.13; CI 1.23-1.57). A subset of 72 subjects was studied for FL levels. FL was significantly higher in subjects with pathogen positive diarrhea (43.2 ± 47 vs. 83.5±91.8 p=0.02 ANNOVA). Subjects with the CC allele were more likely to have levels below the mean of the entire group when compared to subjects in the CT / TT group (14 vs 42% p=0.032 Fisher's). This study suggests that North American travelers with the LTFEx15 TT genotype are more susceptible to TD than subjects with CT and CC genotypes and that subjects with the CC genotype produce less FL in response to infection.

ABSTRACT

The Effect of Pentoxyfilline on Pulmonary Fibrosis Development in Rats with Cardiac Failure

BRIAN S. HURLBURT The University of Texas at Houston Medical School Class of 2009

Sponsored by: Marie-Francoise Doursout, PhD, Department of Anesthesiology
Supported by: Marie-Francoise Doursout, PhD, Department of Anesthesiology
Key Words: pentoxyfilline (PTX), pulmonary fibrosis, IL-6, IL-8

Pulmonary fibrosis/edema is a common and often serious complication in patients with heart disease. We hypothesized that elevated vascular pressures could stretch the pulmonary vessels and cause the release of cytokines which would lead to the development of fibrosis. Our study was an in vivo analysis designed to determine whether pentoxyfilline (PTX) plays a protective role against the development of pulmonary fibrosis by suppressing the production of inflammatory cytokines IL-6 and IL-8 in rats with prolonged elevated left atrial pressure (LAP). PTX, a methlyxanthine derivative, has been reported to modulate the production of cytokines IL-6 and IL-8. Our experimental design included the insertion of a wire through the left ventricle which restricted left ventricular filling during cardiac diastole. This caused an increase in LAP of about 15-20 mm Hg above baseline. Rats were allowed to recover for at least a week, and then were divided into 3 groups. Group 1 was sham control and was not subjected to elevated LAP. Group 2 rats were subjected to elevated LAP for seven days and received no treatment, whereas Group 3 rats were subjected to elevated LAP and treated with PTX at a dosage of 5 mg/kg/hr over seven days. Inflammatory cytokines (IL-6 and IL-8) were measured in bronchoaveolar lavage (BAL) fluid using ELISA. BAL fluid samples from rats treated with PTX showed significant decreases in IL-6 and CRO/CINC-1 (the murine derivative of IL-8) by 96% and 86%, respectively. Our data demonstrate that PTX is a potent cytokine (IL-6 and IL-8) inhibitor, likely through the nuclear factor kappa B (NF-kB) pathway. However, the involvement of this pathway remains to be established. In conclusion, PTX could be used as a potential suppressor of inflammatory cytokines and help reduce lung fibrosis development in patients with heart disease.

ABSTRACT

What are the Molecular Mechanisms for the COX-2 Inhibitors Risky to Heart Disease?

REBECCA JENTZEN The University of Texas at Houston Medical School Class of 2009

Sponsored by: Ke-He Ruan MD, PhD, Department of Internal Medicine/Hematology
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: *cyclooxygenase-1 (COX-1), arachidonic acid (AA), prostacyclin or prostaglandin I_2 (PGI_2), PGI_2 synthase (PGIS), thromboxane A_2 (TXA_2)*

Thromboxane A2 causes platelet aggregation and vascular constriction. Conversely, prostacyclin counters these effects and is considered one of the major vasculoprotective mediators. Biosynthesis of these two mediators is coupled through the cyclooxygenase pathway which produces a common intermediate, PGH_2, which is rapidly isomerized by either TXAS or PGIS. The goal of this project is to upregulate the production of PGI_2 from the shared intermediate to effectually decrease the amount of PGH_2 that can be converted to TXA_2 in order to promote a healthy vascular system and decrease ischemia. The PI has discovered through 3-D solution structures that PGIS is anchored in the ER membrane by its N-terminal domain. They have also discovered that COX-2 and PGIS are likely closer together than COX-1 and PGIS. An active, single fusion protein enzyme containing COX-2 and PGIS protein sequences (COX-2-linker-PGIS) was created that continually converted AA to PGI_2 through three steps. However, COX-1 would be a more ideal pathway and safer for gene and cell therapies because it is a house keeping enzyme and has less pathological implications than COX-2. A COX-1-PGIS fusion enzyme (COX-1-linker-PGIS) was created with 10 amino acids as the transmembrane domain, constructed from bovine rhodopsin which is identical to human rhodoopsin, which linked the C-terminus of COX-1 to the N-terminus of PGIS. The High Performance Liquid Chromatography assay results showed no increase in activity; however, there was an increase of PGI_2 production in the COX-2-linker-PGIS. This observation indicated that the COX-1 C-terminal domain has an integral function in the process of converting AA to PGH2. To create an active fusion enzyme containing COX-1 and PGIS, an alternative approach is needed. A reversed linkage connecting the C-terminus of PGIS to COX-1 through the linker is suggested by the studies.

ABSTRACT

The use of Genetically Altered Sortase Genes to Identify Phenotypic Changes that Might be Associated with Virulent Strains of *Enterococcus faecalis*

KELVIN KEMP The University of Texas at Houston Medical School Class of 2010

Sponsored by: Barbara Murray, M.D. Department of Internal Medicine
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: *Sortases, immunofluorescence, biofilm, deletion mutants*

Background: Some enterococcal strains are known as multi-drug resistant opportunists which cause difficult to treat hospital acquired infections. Studies have shown that enterococci can (presumably via its putative and known adhesins) attach to extracellular matrix proteins like collagen and fibrinogen which likely is important for virulence. Sortases are enzymes which are known to "sort" certain proteins (as shown for adhesins in other species) and attach them to the cell wall.
Methods: Mutant derivatives of *E. faecalis* OG1RF with one or both of its sortase genes deleted (*srtA*, *srtC*, *srtA-srtC)* were generated and then confirmed for deletions using colony lysates, DNA hybridization, PCR and pulsed field gel electrophoresis. Each derivative was analyzed for localization of the adhesin protein EF2505 on the cell surface using immunofluorescence microscopy (IFM) using anti-EF2505 antibody (previously raised in rabbits using recombinant EF2505) and anti-rabbit FITC. Each derivative was also compared to OG1RF for biofilm formation using a previously described method.
Results: Extensive observation in IFM did not show a difference between OG1RF and the derivatives. This indicates that immunofluorescence does not depend on a protein being correctly anchored to cell wall. OD_{570} medians from biofilm assays of *srtA* deletion mutant (0.89, interquartile range (IR), 0.82 to 0.92), *srtC* deletion mutant (0.47, IR, 0.41 to 0.54) and the *srtA-srtC* double deletion mutant (0.22, IR, 0.18 to 0.27) were compared with appropriate control strains of OG1RF (0.96, IR, 0.92 to 1.0) using Kruskal-Wallis test (ANOVA) and $P < 0.0001$ was considered significant.
Conclusion: (1) IFM was not helpful in distinguishing sortase mutants from wild type OG1RF, at least for the protein tested. (2) The reduction in biofilm by the double mutant appeared greater than the sum of the individual mutants, suggesting that functional substitution by the sortases may occur. Which proteins are affected by the sortases remains to be determined.

ABSTRACT

Hypertonic Saline Redistributes Intestinal Tissue Water and is associated with Aquaporin 4 Upregulation

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Sponsored by: R.S. Radhakrishnan,MD; H. Xue, MD; S.J. Allen, MD: Charles S. Cox Jr., MD; Department of Surgery/Pediatric

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14

Key Words: Intestine, edema, HS, Aquaporin

Introduction: We have shown that acute edema induced by resuscitation and mesenteric venous hypertension (MV-HTN) impairs intestinal transit and contractility. In addition, we have shown that pretreatment and post treatment with hypertonic saline (7.5% HS) preserves intestinal tissue water and improves intestinal transit. Aquaporins are a family of pore forming membrane proteins that are vital in water transport across cellular membranes. Preliminary work with microarrays in the setting of acute intestinal edema has shown that aquaporins 2 and 4 show increased expression with hypertonic saline administration. We hypothesized that hypertonic saline given after acute intestinal edema improves intestinal tissue water concentration by upregulation of aquaporins 2 and 4.

Methods: Rats were randomized to four groups: sham, MV-HTN with 80 cc/kg NS (NS 80), HS alone, and NS 80 with HS administration after 30 minutes. Rats were placed in metabolic cages to measure urine output. After 6 hours, rats were sacrificed and intestinal edema was measured by wet to dry tissue weight ratio (W/D). In addition, peritoneal fluid and small intestine intraluminal fluid were measured. Next, samples of rat ileum were assessed for levels of aquaporin 2 and 4 via Western blot analysis.

Results:

	Sham	NS 80	HS alone	NS80 + HS	Units
W/D	3.58±0.05†	4.07±0.15‡	3.52±0.08†	3.71±0.10†	Ratio
Urine	1.40±0.27†	1.64±0.33†	1.65±0.44†	3.03±0.69*	mL
Intraluminal Fluid	0.82±0.22†	1.38±0.18‡	0.67±0.10†	2.07±0.4*	mL
Peritoneal Fluid	0.19±0.05†	0.55±0.07‡	0.14±0.03†	0.87±0.14*	mL
Aquaporin 2	10.7±2.0†	38.9±7.8‡	49.7±9.9‡	46.4±12.4‡	Rel Units
Aquaporin 4	0.54±0.03†	0.35±0.01‡	0.49±0.03†,*	0.43±0.01*	Rel Units
Different symbols (†,‡,*) indicate statistical significance, $p<0.05$					

NS 80 causes a significant increase in tissue edema. HS administration causes a significant decrease in tissue water and a significant increase in urine, intraluminal, and peritoneal fluid volume. These changes are associated with a significant increase in aquaporin 4 expression.

Conclusion: HS prevents intestinal tissue edema formation and redistributes fluid to the intravascular, intraluminal, and peritoneal spaces. While the complete mechanism of action of HS is unclear, aquaporin 4 may play a significant role in the improvement of intestinal edema.

ABSTRACT

Induction of β-Lactamase Activity by *Bacillus anthracis*

ROBERT J. LENTZ The University of Texas at Houston Medical School Class of 2009

Sponsored by: Theresa M. Koehler, PhD, Department of Microbiology and Molecular Genetics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: *Bacillus anthracis*, beta-lactamase, beta-lactam, antibiotic resistance

Bacillus species are commonly resistant to penicillin and other β-lactam antibiotics due to β-lactamase synthesis. *Bacillus anthracis*, the causative agent of anthrax, possesses two genes, *bla1* and *bla2*, which encode functional β-lactamase enzymes. Nevertheless, prototypical strains are susceptible to penicillin, the most accessible therapeutic for anthrax worldwide. Rare isolates of *B. anthracis* are reported to be penicillin-resistant. At least one of these strains, 31-103, contains specific mutations outside of the *bla* loci that render constitutive expression of the *bla* genes. Some *Bacillus* species can be induced to express β-lactamase activity under stressful conditions. We hypothesized that β-lactamase activity could be induced in a prototypical penicillin-susceptible *B. anthracis* strain, 9131, by exposing it to compounds reported to induce β-lactamase activity in closely-related species. We cultured *B. anthracis* 9131, *B. cereus* 10987, and *B. thuringiensis* 97-37 in media containing *Bacillus* peptidoglycan, sublethal concentrations of various β-lactam antibiotics and bacitracin, and in high phosphate and high temperature growth conditions. β-lactamase activity was assessed using the nitrocefin test. No significant increases in *B. anthracis* β-lactamase activity were observed. As expected, *B. cereus* 10987 β-lactamase activity was induced by penicillin G (73-fold increase after two hours), dicloxacillin (6-fold increase), and bacitracin (12-fold increase). Induction in *B. thuringiensis* was also accomplished with penicillin G (8-fold increase) and dicloxacillin (5-fold increase). These data support a model in which a *trans*-acting pathway required for induction of β-lactamase activity is disabled in *B. anthracis* but intact in *B. cereus* and *B. thuringiensis*.

ABSTRACT

FtsA Derivatives Bypass Other Proteins of the *Escherichia coli Divisome*

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Sponsored by: William Margolin, Ph.D, Department of Microbiology and Molecular Genetics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: FtsA, T215A, tandem dimer fusion, divisome

In *Escherichia coli*, FtsA and ZipA proteins tether the tubulin-like FtsZ protein to the cell membrane at midcell to form a transmembrane divisome complex prior to cytokinesis. FtsN, a transmembrane protein, is recruited to the divisome last and, like FtsZ, FtsA and ZipA, is essential for viability. Previous studies have shown that gain of function mutants of FtsA could compensate for the loss of ZipA or FtsN, but the mechanisms underlying these bypasses are largely unknown. FtsA forms dimers and exists both in a membrane-bound unphosphorylated state and in a cytoplasmic phosphorylated state, but the relevance of these properties to cell division function remains unclear. We hypothesized that enhancing the dimerization and/or membrane-binding properties of FtsA might also result in a gain of function, and if so, would suggest a mechanism. Two FtsA derivatives, a T215A mutant and a tandem dimer fusion, were tested for their ability to permit viability in the absence of ZipA or FtsN. The T215A mutant cannot be phosphorylated and consequently remains bound to the cytoplasmic membrane, while the FtsA tandem dimer fusion cannot exist as a monomer. We found that the membrane-bound T215A derivative bypasses the need for FtsN, and, remarkably, the FtsA tandem dimer can compensate for the loss of ZipA but not FtsN. These results suggest that biasing FtsA towards a membrane-bound dimer stabilizes the divisome complex via distinct mechanisms.

ABSTRACT

Oxidative Effects of Celastrol in the Yeast *Sacchromyces cerevisiae*

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Sponsored by: Kevin A. Morano, Ph.D., Department of Microbiology & Molecular Genetics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Heat Shock, Celastrol, Oxidative Stress

Celastrol is a triterpenoid bioactive compound isolated from the Chinese Thunder of God vine (T. wilfordii) which has been shown to activate the heat shock response in the yeast *Saccharomyces cerevisiae* as well as human cells. This is achieved through activation of the heat shock transcription factor 1 (HSF1) with kinetics paralleling those of heat stress. In addition, celastrol induces the transcription of dozens of oxidative stress genes through activation of the redox-sensitive transcription factor Yap1 in yeast. I therefore set out to determine the interplay between celastrol treatment and oxidative damage. First, a standard "kill" curve was developed to determine the proper concentration of the lethal oxidant hydrogen peroxide. Subsequently, cultures were treated with appropriate concentrations of celastrol and peroxide together or sequentially, with treatments of one hour. In contrast to the expected effect of cytoprotection, a synergistic killing effect was seen when the two treatments were combined. After treatment with celastrol alone, approximately 81% viability was seen. With 3 mM peroxide viability dropped to 7.4% and with the two treatments combined viability was 0.98%. This suggests that celastrol may be sensed as an independent oxidative stress, and further experiments are planned to evaluate this hypothesis. Furthermore, we are working to determine if celastrol treatment can mimic sub-lethal oxidative stress in conferring resistance to subsequent lethal exposure.

ABSTRACT

Effect of Meropenem (MPM) and Aztreonam (AZT) with and without Variable Concentrations of Colistin (CO) on Metallo-β-Lactamase (MBL) Producing *Pseudomonas aeruginosa*

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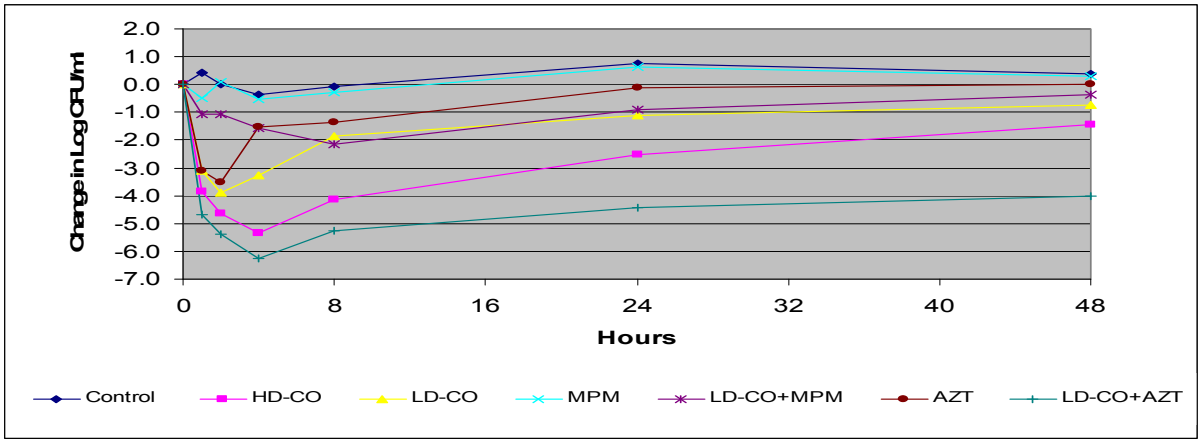
Sponsored by: John Mohr, PharmD, Department of Internal Medicine/Infectious Diseases
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Colistin, Aztreonam, Meropenem, MBL, *P. aeruginosa*

Background: MBL producing *P. aeruginosa* are a growing public health threat and limited therapeutic options are available.
Methods: *P. aeruginosa* containing unique MBLs (VIM-2, VIM-7, GIM-1, SPM-1) were identified. MICs for CO, MPM, and AT were determined by Etest ®. The bactericidal effect of high-dose colistin (HD-CO), low-dose colistin (LD-CO), MPM, LD-CO+MPM, AZT and LD-CO+AZT was tested in a one compartment, *in-vitro* pharmacodynamic model, mimicking human pharmacokinetics. The organisms were incubated overnight and diluted to yield 10^9 CFU/ml. Drugs were administered into the central compartments to achieve free peak concentrations of HD-CO:20 µg/ml, LD-CO:10 µg/ml, MPM:100 µg/ml, and AZT:100 µg/ml. Drugs were administered every 8 hours for 48 hours and a 2-hour half-life was modeled by pumping media through the central compartments. Samples for colony counts were obtained at 0,1,2,4,8,24, and 48 hours. A $3\log_{10}$ reduction in CFU/ml from baseline at 24 and 48 hours was considered significant.
Results: All strains were susceptible to CO and resistant to MPM. VIM-7, GIM-1, SPM-1 were non-susceptible to AZT. The mean change in CFU/ml was < $3\log_{10}$ at 24 and 48 hours for all regimens tested except LD-CO+AZT. LD-CO+AZT had a > $4\log_{10}$ reduction at 24 hours that was sustained at 48 hours. This effect was organism dependent as VIM-7 only demonstrated a $1.1\log_{10}$ reduction at 24 hours.



Conclusions: LD-CO in combination with AZT yielded the greatest *in*-vitro activity against MBL producing *P. aeruginosa*.

ABSTRACT

Improved Systemic Metabolism and Skeletal Muscle Gene Expression Nine Months After Bariatric Surgery

CHARLES L. MAJKA The University of Texas at Houston Medical School Class of 2009

Sponsored by: Heinrich Taegtmeyer, MD, DPHIL, Department of Internal Medicine/Cardiology
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Insulin Resistance, Obesity, Skeletal Muscle, Fatty Acid Metabolism, Bariatric Surgery

Background: Bariatric surgery is a non-pharmacologic form of sustained weight loss and corrects many of the metabolic disturbances associated with obesity. We tested the hypothesis that weight loss following bariatric surgery results in improved glucose and lipid metabolism and is associated with changes of metabolic gene expression in skeletal muscle.
Methods: Twenty-five severely obese individuals (BMI>35) were enrolled prospectively prior to bariatric surgery. Physiologic and metabolic profiles, including skeletal muscle (vastus lateralis) biopsies, were obtained at the time of surgery and at nine months post-operatively. These biopsies were analyzed for changes in the levels of metabolic gene transcripts using quantitative real time polymerase chain reaction (Q-PCR) analysis.
Results: The patients' mean weight decreased from 141.01 kg to 105.01 kg (% change: -26%, $p<0.0001$). Using repeated measures ANOVA we found significant decreases in the transcript levels of Stearoyl-CoA desaturase and pyruvate dehydrogenase kinase 4 (percent change: -85% and -90%, respectively, $p<0.0001$). We also found decreases in the transcript levels of peroxisome proliferator activator receptor alpha regulated genes: carnityl palmitoyltransferase 1, medium chain acyl-CoA dehydrogenase, and uncoupling protein 3 (-26% $p<0.05$, -43% $p<0.001$, and -52% $p<0.0001$, respectively). Concurrent with these changes were improvements in systemic glucose (-29%, $p=0.006$), insulin (-54%, $p<0.0001$), and free fatty acid (-17%, $p=0.017$) levels.
Conclusions: The systemic derangements of glucose and fatty acid metabolism normalized with bariatric surgery in patients with clinically severe obesity. Furthermore, the changes in the expression of genes responsible for fatty acid partitioning, glucose oxidation and fatty acid oxidation are consistent with increased oxidative metabolism.

ABSTRACT

Effects of Histamine on Dopamine Release from Rat Retina

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Sponsored by: David Marshak, PhD, Department of Neurobiology and Anatomy
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Dopamine(DA), Histamine (HA), High Pressure Liquid Chromatography (HPLC)

The goal of these experiments was to learn how input from the brain influences the processing of visual information in the retina. Rat eyecups (n=38) were maintained *in vitro* and exposed to HA, one of the neurotransmitters in the pathway, and its effect on DA release was measured. My hypothesis was that HA inhibits the release of DA from the retina. Experiments were done with a constant background light and began with 60 min of superfusion to allow the retina to recover from surgery. The eye cups were superfused with Ames medium containing pargyline 10μm (DA degradation blocker) and nomifensine 1μm (inhibitor of DA uptake) equilibrated with 95%O_2/5%CO_2. To study the effects of HA (1, 5 and 10μm) on basal DA release, HA was applied for 20 min followed by a 50 min washout. To study HA's effect on light stimulated release, the experiments were repeated with a 3 Hz flashing light during HA application. Histamine was omitted in the control experiments. Samples were collected in test tubes containing 1M $HClO_4$, 200μm ascorbic acid (to minimize DA oxidation), and 20μm 3,4 dihydroxy benzylamine (internal standard). Samples were concentrated using a solid phase extraction method, and DA was measured by HPLC with electrochemical detection. The samples appear to contain DA, but it is at or below the limit of detection. These results are based on the analysis of 20μL; later we will concentrate the samples and use a new detector to increase the sensitivity of the assay.

ABSTRACT

Role of Thioredoxin-Interacting Protein (TXNIP) in Diabetic Nephropathy

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Sponsored by: Constance Albarracin, MD, PhD, Department of Pathology, UT at Houston Graduate School of Biomedical Sciences

Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T35 DK007676-14

Key Words: TXNIP, diabetes, nephropathy

Hyperglycemia-induced oxidative stress has been suggested to be a critical factor in diabetic end-organ damage. Recent work has identified thioredoxin-interacting protein (TXNIP) to be involved in diabetes. TXNIP induces oxidative stress and its expression is induced by glucose in different rodent cells. Hyperglycemia induces TXNIP expression in kidney, pancreatic islets and aorta smooth muscle. To determine whether glucose increases TXNIP expression in major organs affected by diabetes in humans, we measured TXNIP expression in human 293 kidney cells, human islets as well as human cardiac muscle samples. Interestingly, incubation at high glucose led to a significant increase in TXNIP expression in 293 kidney cells and in isolated islet cells. Cardiac muscle samples from diabetic patients had a >4-fold higher TXNIP expression compared to non-diabetic subjects, as measured by real-time RT-PCR and confirmed by Western blot analysis. In addition, studies also indicate that TXNIP may be involved in the formation of fibrosis associated with diabetic nephropathy. To address this, additional studies are in progress to evaluate the expression of TXNIP at different stages of diabetic nephropathy using archival paraffin sections from diabetic patients. In summary, the induction of TXNIP expression by hyperglycemia suggests a critical role for this protein in mediating some of the toxic effects of hyperglycemia that lead to diabetic complications including diabetic nephropathy.

ABSTRACT

MRI Findings in Pediatric Head Trauma Patients After Hypertonic Saline Treatment

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Sponsored by: Stephen A Fletcher, DO, Department of Neurosurgery/Pediatric
Supported by: Memorial Hermann Hospital
Key Words: Hypertonic saline, myelinolysis, magnetic resonance, pediatric, trauma

Osmotic demyelination syndrome (ODS), within the context of hypertonic saline (HS) treatment for elevated intracranial pressure (ICP) following head trauma, in the pediatric population has received relatively little attention. This study reviewed 27 pediatric cases of head trauma, all of which received HS to regulate elevated ICP. 18 of these 27 patients had magnetic resonance (MR) imaging of their brain done and were, therefore, selected to have their imaging studies re-read by a certified neuroradiologist employing diffusion tensor imaging, magnetization transfer imaging and double inversion techniques. Other data, including serum sodium concentrations ([Na]), age and Glascow Coma Score, have been collected and analyzed with respect to the MR findings. During the first day of treatment, each patient had a [Na] rise, from baseline before HS, ranging from 3 to 40 mEq/L (mean = 17 mEq/L) over an average of 23 hr (SD = 4 hr). Even though the [Na] was raised far faster than current adult recommendations have stated, only 1 of the 18 patients exhibited any kind of abnormal MR signal from the pons or central white matter. Myelinolysis could not be excluded in this case, but it is unlikely to be the explanation for the abnormal signal. None of the patients had chronic conditions or significant past medical history, aside from one child testing positive for cocaine at birth. As far as the evidence leads from this study, it seems that this treatment does not produce myelinolysis; but in order to draw clinically significant conclusions, a larger study needs be conducted.

ABSTRACT

Comparative Analysis of Structural and Functional Characteristics of Essential Brain Regions as Measured by Functional Imaging and Electrophysiology

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Sponsored by: Nitin Tandon, MD, Department of Neurosurgery
Supported by: Department of Neurosurgery, University of Texas Health Science Center at Houston Medical School
Key Words: language mapping, functional magnetic resonance imaging; electrophysiology

Purpose**:** A battery of language tasks administered during functional magnetic resonance imaging (fMRI) of the brain was used to generate a map of cortical regions "essential" for language production in a population of normal subjects. Ongoing work will compare language sites determined by fMRI with cortical stimulation mapping (CSM) data in neurosurgical patients undergoing mapping using sub-dural electrodes.
Methods: Functional data using a battery of language tasks were acquired in four normal subjects. This battery (object naming, action naming, proper naming, word-stem completion, and auditory comprehension) was developed to localize "critical" language areas. A block design fMRI paradigm, using concurrent volumetric echo-planar imaging on a 3T Phillips scanner was used. Data were processed using AFNI software. Functional data were registered to an anatomical MRI of the subject and the dataset was transformed into standardized space. Average activation maps of the population were then generated.
Results: Activation of the anterior language areas (Broca's area) was detected during the word stem completion and action naming tasks. Prominent activation of the superior temporal gyrus and the temporo-parietal junction (Wernicke's area) was noted during the auditory comprehension task. Comparisons of the activation maps produced during naming of objects versus people revealed activation of the fusiform face area.
Conclusion: The results obtained from this population suggest that this battery of tasks used to map language with fMRI is a valid measure for determining language loci in the human brain. This provides us with a foundation with which to evaluate concordance between CSM and fMRI.

ABSTRACT

A Review of Hypersonic Saline: Physiology, Benefit and Limitations

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Sponsored by: Charles Cox, M.D., Department of Surgery/Pediatric
Supported by: Charles Cox, M.D., Department of Surgery/Pediatric
Key Words: Hypertonic saline, osmotherapy, intracranial pressure management

Proper management of elevated intracranial pressure (ICP) and cerebral edema is essential in treatment of acute traumatic brain injury (TBI). A clinical case of TBI can quickly become complicated by secondary injury and the development of ischemia, hypoxia, and hypotension, due to the effects of edema and elevated ICP. Intravenous administration of hyperosmolar solutions efficiently reduces ICP and edema by creating an osmotic gradient across the blood-brain barrier (BBB) that pulls fluid from the cerebral parenchyma into the general circulation. The primary goal of studying hyperosmotic solutions in the management of TBI is to find an ideal solution that will counterbalance the pathological disturbances in the volume dynamics of the intracranial compartment while optimizing tissue perfusion and limiting possible detrimental effects on other organ systems.

Since the advent of osmotherapy research almost 90 years ago, mannitol has been considered the hallmark for management of TBI, but recent studies have brought the use of hypertonic saline as an ideal osmotic agent to light. Clinical trials have given support to hypertonic saline treatment in management of ICP and many animal studies have shown that hypertonic saline may impart benefits to other systems of the body. The purpose of this review will be to address basic physiology of osmosis and the blood-brain barrier, to describe the benefits associated with hypertonic saline, and to evaluate certain limitations associated with hyperosmotic therapy.

ABSTRACT

Investigation of Trehalose-6, 6'-Dimycolate-induced Granuloma Formation: A Possible Model for Crohn's Disease

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Sponsored by: Jeffrey K. Actor, PhD, Department of Pathology and Laboratory Medicine
Supported by: Jeffrey K. Actor, PhD, Department of Pathology and Laboratory Medicine
Key Words: Crohn's disease, trehalose-6,6'-dimycolate, *Mycobacterium avium* subspecies paratuberculosis

Although the pathology and morphology of Crohn's disease have been described thoroughly, the etiology of Crohn's granulomatous inflammation is as yet unexplained. The mycobacterial theory, one of three major theories that attempt to explain the pathogenesis of Crohn's disease, suggests that Crohn's may be caused by Mycobacterium avium subspecies paratuberculosis (MAP) via dysregulation of immune regulation and tolerance in the gastrointestinal tract. The mycobacterial surface glycolipid, trehalose-6,6'-dimycolate (TDM or cord factor), has been shown to elicit granulomas that mimic the granulomas seen in infection with various Mycobacterial species. Specifically, TDM-induced granuloma formation is a useful model to study the events involved in the induction of a granulomatous response, and TDM-induced lesions demonstrate many similarities in cytokine response to those identified with Crohn's disease. An examination of the gastrointestinal response to TDM may provide a link between mycobacterial surface components and Crohn's disease. In order to examine this response, wild-type C57Bl/6 mice were gavaged with oil-in-water emulsions containing (25-100ug) TDM or an equal amount of control emulsion without TDM. The mice were subsequently sacrificed at 1, 4, 7, and 14 days and tissues were analyzed with regard to cytokine profiles (Peyer's patches and spleen) and histopathology (gastrointestinal track, spleen, Peyer's patches and mesenteric lymph nodes). Histological examination of tissue showed only minimal inflammatory response, with only minor influx of leukocytes at 1 and 4 days post administration. Inflammatory cytokine profiles were compared using a PCR-based approach, revealing only minor increase in proinflammatory TNF-a and IL-1 mRNA in TDM-gavaged mice.

ABSTRACT

Effect of Hypertonic Saline on Pulmonary Function in Pediatric Patients Treated for Elevated Intracranial Pressure

J. CALEB RICHARDS The University of Texas at Houston Medical School Class of 2009

Sponsored by: Stephen A. Fletcher, DO, Department of Pediatrics/Neurosurgery
Giuseppe N. Colasurdo, MD, Department of Pediatrics/Pulmonary

Supported by: Lawrence H. Robinson, MD, Department of Pediatrics/Radiology

Key Words: Pulmonary function, hypertonic saline, traumatic brain injury

Hypertonic saline treatment could affect pulmonary function in pediatric patients treated for elevated intracranial pressure from traumatic brain injury. Pulmonary function can be assessed by evaluating arterial oxygen pressure (PaO2), fraction of inspired oxygen (FiO2), the calculated PaO2:FiO2 ratio, arterial oxygen saturation (SaO2), and chest x-ray for pulmonary edema. The objective of this study is to evaluate pulmonary function through these parameters and determine if hypertonic saline treatment is a risk toward affecting pulmonary function. The study is a retrospective chart review of 28 patients receiving treatment at Memorial Hermann Children's Hospital. PaO2, FiO2, SaO2, and PaO2:FiO2 values were collected from the charts times and correlated with plasma sodium levels recorded during hypertonic saline treatment. Chest x-rays taken at treatment start, 72 hours after treatment start, and at extubation were scored for pulmonary edema by a pediatric radiologist. The results from the study show that average values for PaO2, PaO2:FiO2, and SaO2 fall within normal ranges. The chest x-ray scores on average show an increase from 0 to 72 hours, and a decrease from 72 hours to extubation. However, the correlation between plasma sodium and these average values was not strong enough to be considered statistically significant. Alteration in these average values is likely to be due to other confounding factors associated with their injury and not the elevated sodium from hypertonic saline treatment. In conclusion, pulmonary function is not negatively affected by hypertonic saline treatment in children with elevated intracranial pressure from traumatic brain injury.

ABSTRACT

Renal Failure Analysis in Head Injury Patients Undergoing Hypertonic Saline Therapy

DANIEL RINEWALT The University of Texas at Houston Medical School Class of 2009

Sponsored by: Stephen Fletcher, DO, Department of Pediatrics/Neurosurgery
Nathan Strobel, MD, Department of Pediatrics
Supported by: Department of Neurosurgery/Pediatric Neurosurgery
Key Words: Hypertonic Saline, Renal, TBI

An elevation in intracranial pressure (ICP) is commonly treated by placing the patient in a hyperosmotic state such that the brain parenchyma is effectively dehydrated, increasing tissue compliance. While many studies have shown the effectiveness of hypertonic saline (HTS) as an osmotic agent for treating traumatic brain injury (TBI), its effect on the renal system has not been studied. Theoretically the induction of a hypernatremic state could damage the kidneys, if this is not the case however HTS may be the most valuable treatment for an elevated ICP. An IRB approved retrospective study of 27 pediatric patients (GCS 3-13) was designed to collect the following parameters: serum sodium, osmolality, creatinine, and blood urea nitrogen (BUN); urine osmolality, hematuria or proteinuria; and ICP and cerebral perfusion pressure (CPP). Increasing the serum sodium was found to lower ICP and raise CPP, a finding previously noted in many publications. Rare creatinine deviations from the normal physiologic range did not correlate with serum sodium, and while BUN measurements were found to digress considerably no relationship with serum sodium could be found statistically. Urine osmolality remained consistently higher than plasma osmolality, indicating the kidneys retained the ability to concentrate the urine. Mannitol, another commonly used osmotic agent, has been shown to increase creatinine levels above the normal range while being less effective in maintaining the target ICP. HTS may very well be a safer and more efficient treatment to lower ICP.

ABSTRACT

Characterization of Proteins and Effectors of the Type IV Secretion System in *Burkholderia cenocepacia* Recovered as Clinical Isolates from Cystic Fibrosis Patients

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Sponsored by: Peter J. Christie, Ph.D., Department of Microbiology and Molecular Genetics
Supported by: National Institute of Diabetes and Digestive and Kidney Diseases, 5 T5 DK007676-14
Key Words: Cystic fibrosis, *Burkholderia cepacia* complex, cepacia syndrome, PtwD4

Cystic fibrosis (CF) is a life threatening genetic disease without a cure. CF patients are extremely susceptible to lung infections and some, like the cepacia syndrome, can prove fatal. The cepacia syndrome is a severe progressive respiratory failure that occurs in 20% of cystic fibrosis patients infected with *Burkholderia cenocepacia* or closely related species. *Burkholderia spp.* are resistant to most antibiotics necessitating the development of new therapeutics. Dr. Gonzales at Texas A&M University has obtained evidence that *B. cenocepacia* uses a type IV secretion (T4S) system to translocate effector proteins to mammalian cells during the infection process. One component of the T4S system, PtwD4, is a member of the VirD4 family of T4S substrate receptors. In the model pathogen *Agrobacterium tumefaciens* under study in the Christie lab, VirD4 functions to recruit DNA and protein substrates to the polar-localized VirB/D4 T4S machine. My studies focused on testing whether PtwD4 also functions as a spatial determinant for substrate docking with T4S machines in *B. cenocepacia* and *A. tumefaciens*. Using molecular techniques, I cloned the wild-type *ptwD4* gene and derivatives fused to the green fluorescent protein (GFP) and a FLAG epitope behind suitable promoters for *in vivo* studies of PtwD4 function and subcellular localization. I am also preparing constructs designed to characterize translocation of putative effectors through the *B. cenocepacia* PtwD4 T4S system during infection of the mammalian cell. Results of these studies will stimulate development of novel therapeutic strategies directed at suppressing the action of T4S machines in *Burkholderia spp*.

ABSTRACT

Evaluation of Colloid Administration in Fluid Resuscitation of Major Thermal Injuries

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Sponsored by: David J. Wainwright, MD, Department of Surgery/Plastic
Supported by: Donald H. Parks, MD, Department of Surgery/Plastic
Daniel J. Freet, MD, Department of Surgery/Plastic
Timothy C. Hollenbeck, MD, Department of Surgery/Plastic
Key Words: Burn; total body surface area; fluid resuscitation; Parkland Formula

Introduction: Burn patients require a substantial amount of intravenous fluid administration for adequate resuscitation following their injury. The objective of this study was to investigate whether or not burn patients who received colloid during resuscitation showed a decrease in their fluid requirements during the first 48 hours post injury.
Materials and Methods: A retrospective chart study was performed of 35 patients who sustained >30% burns. Data was reviewed and included age, weight, gender, % total and 3rd degree burn, etiology, presence of inhalation injury, associated medical problems, time of injury to burn unit admission, and whether or not they received colloid. Hourly fluid inputs (volume and type) and output (urine and GI losses) was recorded for each patient.
Results: By comparing the two patient sets (receiving and not receiving colloid), we evaluated the actual volume administered and that calculated by the Parkland Formula. Our findings showed that the colloid patients received a slightly larger volume of fluid than the crystalloid patients. Also, the crystalloid patients had a higher urine output than the colloid patients.
Conclusions: Our results indicated patients who received colloid within the first 48 hours post burn did not require a significantly lower total fluid volume administration during resuscitation compared to those patients who were given only crystalloid.

ABSTRACT

Evaluation of Minimally Invasive Approaches to Metopic and Coronal Craniosynostosis

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Sponsored by: John Teichgraeber, MD, Department of Surgery/Pediatric
Supported by: John Teichgraeber, MD, Department of Surgery/Pediatric
Key Words: Microscopic, craniosynostosis, metopic, coronal, molding helmet therapy

Craniosynostosis occurs when the bony sutures of an infant's skull close prematurely. This results in impaired bone growth perpendicular to the affected suture and which results in a misshapen head and increased intracranial pressure. The purpose of this study is to evaluate a minimally invasive surgical approach. The technique uses a surgical microscope and a strip craniectomy of metopic and coronal synostosis with subsequent molding helmet therapy. Between May 2001 and January 2006, 16 patients were treated using this technique. In this group there were 4 metopic, 5 bicoronal, and 7 unicoronal patients. The control group was treated using an open cranial reconstruction. Preliminary data suggests that operating time, blood loss, transfusion rate, hospital stay, and ICU stay are all similar or lower using the microscopic approach. Average age of microscopic patients was 16 ± 9 weeks compared to 40 ± 23 weeks in the control. Surgical times for metopic, bicoronal, and unicoronal surgeries were 57±22 (vs 195±26) min, 135±55 (vs. 232±55) min, 73±30 (vs. 242±22) min respectively. Similarly, blood losses were 115±82 (vs. 112±82) cc, 45±9 (vs. 412±195) cc, 38±10 (vs. 370±160) cc. All Microscopic patients stayed 1 day in the ICU vs 1.8±1.6 days for controls. Overall hospital stays were 1.75±0.75 days for microscopic patients vs. 5±3 days for controls. Further research is being conducted to evaluate aesthetic outcome of microscopic strip craniectomy with head molding therapy compared to open cranial vault reconstruction.

ABSTRACT

First Place Winner, 2006 Frank Webber Prize for Student Research

The Role of Interleukin-6 and Complement C5 in the Formation of Granulomas in Response to Mycobacterial Cord Factor Trehalose 6,6'-Dimycolate

KERRY J. WELSH The University of Texas at Houston Medical School *Class of 2009*

Sponsored by: Jeffrey Actor, PhD., Department of Pathology and Laboratory Medicine
Supported by: Regulation of Cortisol by Mycobacterial Glycolipid TDM, NIH-NHLBI R21-HL080313-01
Key Words: Trehalose-6,6'-dimycolate; IL-6; C5; granuloma; tuberculosis

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 IL-6 and complement C5 in the initiation and maintenance of granuloma formation in the TDM model are unknown. Therefore, mice deficient in IL-6 and C5, along with defined wild-type 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. Wild-type C57BL/6 mice demonstrated the formation of granulomas that correlated with increased production of IL-1β, IL-6, MIP-1α, and TNF-α. In contrast, the C5-deficient mice exhibited an exacerbated proinflammatory response that did not culminate in granuloma formation. These mice demonstrated markedly increased production of IL-1β, IL-6, MIP-1α, and TNF-α, with decreased synthesis of IL-12 compared to the complement sufficient wild-type mice. 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 deficient mice also demonstrated an early and markedly increased production of IFN-γ with a corresponding decrease in IL-4 as well as enhanced production of IL-1β, IL-12, MIP-1α, TNF-α, and IL-10 in comparison to the wild-type mice. These data lead to the overall hypothesis that complement C5 is critically involved in the initiation of granulomatous response, whereas IL-6 is important for granuloma maintenance once established.

ABSTRACT

Comparison of Ambu® AuraOnce™ and LMA Unique™ as an Intubation Conduit in Patients Undergoing Elective Surgery

DARRELL W. WILCOX *The University of Texas at Houston Medical School* *Class of 2009*

Sponsored by: Carin A. Hagberg, M.D., Department of Anesthesiology
Supported by: Ambu, Inc.
Carin A. Hagberg, M.D., Professor, Department of Anesthesiology
Key Words: AuraOnce, Ambu, LMA-Unique, laryngeal mask

Purpose: The Laryngeal Mask Airway (LMA) is a supraglottic airway device used to secure the airway for failed laryngoscopic intubations. An endotracheal tube (ET) can be exchanged with the LMA by the use of an Aintree Intubation Catheter (AIC) with fiberoptic bronchoscopy. This study compares the new Ambu® AuraOnce™ LMA to the established LMA-Unique™ as an intubation conduit using a fiberoptically guided AIC. The hypothesis is that the AuraOnce™ LMA is as safe and will perform as well, or better than the LMA-Unique™.
Methodology: This prospective, randomized clinical study enrolled sixty-two adult surgical patients who received either a LMA-Unique™ (n=31) or an AuraOnce™ (n=31). Following LMA placement, an AIC was fiberoptically placed through the shaft of the LMA into the trachea. The LMA was then removed, and an ET was then placed over the AIC using direct laryngoscopy. The time to insert the LMA, AIC and ET intubation was recorded. The number of attempts, seal pressures, and any intraoperative complications were also recorded. All patients were interviewed 2 and 24 hrs postoperatively for evidence of sore throat, hoarseness or dysphagia.
Results: Both devices had similar insertion times, number of attempts, intraoperative and postoperative events. However, the seal pressures were significantly higher with the AuraOnce™ (24.2 ± 4.97) as compared to the LMA-Unique™ (20.3 ± 6.05).
Conclusion: The AuraOnce™ is comparable to the Unique as an intubation conduit using a fiberoptically guided AIC. Additionally, higher seal pressures with the AuraOnce™ may be beneficial for ventilation prior to the exchange.

ABSTRACT

Development of an *In-vitro* Model for *Staphylococcus aureus* Biofilms on Orthopaedic Devices

STEPHEN J. WINSLOW *The University of Texas at Houston Medical School* *Class of 2009*

Sponsored by: Heidi Kaplan, PhD, Department of Microbiology and Molecular Genetics
Supported by: Heidi Kaplan, PhD, Department of Microbiology and Molecular Genetics
Key Words: *Staphylococcus aureus*, biofilm, orthopaedic, bone cement, antimicrobials

Total joint replacement surgeries have a 2% incidence of infection in the roughly 600,000 cases preformed annually in the U.S. These infections generally require treatment, often involving two additional surgeries for removal and replacement of the orthopedic device. *Staphylococcus aureus* is the leading etiologic agent of these infections and is normally found growing on orthopaedic biomaterial surfaces within a matrix termed a biofilm. These biofilm bacteria have been found to be 10 to 1,000 times more resistant to antimicrobials than planktonic cells. An *in-vitro* model of a *S. aureus* osteomyelitis biofilm infection was developed for use in studies to evaluate the effectiveness of various antibiotics against these biofilms. The ATCC 49230 *S. aureus* strain isolated from an osteomyelitis patient was used. To simulate the intra-articular milieu, a synthetic synovial fluid (SSF) was developed. Wafers of polymethyl methacrylate (PMMA) termed bone cement, a commonly used orthopaedic biomaterial, were the substrate for biofilm growth. Each biofilm was generated by incubation of the bacteria and wafers in a static microtiter dish at 37^{o}C and 5% CO_2. The SSF was changed every 24 hrs, taking care not to disturb the biofilm. Crystal violet dye was used to quantitate the total biofilm biomass. For more detailed analysis, confocal laser scanning microscopy was used to generate a three dimensional image that was analyzed using the COMSTAT computer program. This provided data for total biomass, thickness, roughness, and surface area. This model biofilm will now be used to quantitate the action of various antimicrobials on *S. aureus* biofilm growth.

ABSTRACT

Bony Deformities in Hypophosphatemic Rickets

KYLE R. WOERNER *The University of Texas at Houston Medical School* *Class of 2009*

Sponsored by: Allison Scott, MD, Department of Orthopaedic Surgery *and* Shriners Orthopedic Children's Hospital
Supported by: Thomas E. Cain Medical Research Fellowship
Key Words: hypophosphatemic rickets, genu varum, genu valgum, natural history

Hypophosphatemic rickets patients have a proximal tubule reabsorption deficiency for phosphates in the kidney as well as a decreased ability to regulate vitamin-D. This metabolic disease presents with orthopedic sequelae in the form of genu varum and genu valgum. This study was designed to 1) quantify these defomities and view the natural history of this disease with metabolic treatment, 2) observe differences between treatment with active and inactive vitamin-D, and 3) to investigate the incidence of orthopedic surgical intervention over the past three decades at SHC in Houston. In this retrospective cohort study, the charts of children with all forms of hypophosphatemic rickets were reviewed. Measurements were taken in a series of x-rays for each patient that quantified the genu varum and genu valgum in the femur, tibia, and the total leg. Of the 101 patients matching the diagnosis search, 54 fulfilled the criteria of having hypophosphatemic rickets, at least 3 serial x-rays, and at least one x-ray prior to skeletal maturity. The patients studied all showed a significant improvement in their total leg defomities with metabolic treatment. The femoral deformities were significantly greater at presentation, and the most improvement occurred in the femur, with the tibia and femur both having significant improvement individually. The mechanical axis deviation also showed significant improvement. Active vitamin-D did not appear to reduce the genu varum and genu valgum more than the active form. The incidence of surgery at Shriners has stayed fairly constant over the last three decades. In conclusion, this natural history study showed that metabolic treatment has an overall positive effect on the bony deformities in children with hypophosphatemic rickets.

ABSTRACT

The Role of Nuclear Factor – Kappa B in Edema Induced Intestinal Dysfunction

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

Supported by: Charles Cox, MD, Department of Surgery/Pediatric

Key Words: NF-kB, intestinal dysfunction, intestinal edema, PDTC, STAT-3

Intestinal edema is a common condition developed after use of resuscitation fluids in trauma surgery which can lead to a decrease in intestinal motility. A study was designed to determine 1) if edema induced intestinal dysfunction exhibited elevated activation of the transcription factor, nuclear factor-kappa B (NF-kB), 2) if pyrrolidinedithiocarbamate (PDTC), a NF-kB inhibitor, would attenuate the effects of edema induced intestinal dysfunction as observed through intestinal contractility, 3) and if inhibition of NF-kB would show decreased activation of STAT-3, a transcription factor that has been found to interact with NF-kB. Thirty-five male Sprague Dawley rats were randomly assigned to either a sham surgery CONTROL or RESUS+VH group. Edema was induced in RESUS+VH group by a combination of fluid administration and superior mesenteric venous constriction. Rats in both groups were treated with a saline vehicle or PDTC (Sigma-Aldrich, 100 mg/kg, IP) 30 minutes before surgery. Rats were sacrificed 6 hours after surgery and samples were collected from the distal third of the small intestine for transcription factor and contractile activity studies. A significantly greater NF-kB activation was observed in the RESUS+VH group compared to the control (5.51±1.75 vs 11.67±2.34 ng/mg protein, $p<0.05$). PDTC treatment of RESUS+VH rats attenuated edema-induced decreases in intestinal contractile activity compared to RESUS+VH treated with saline (107.28±19.28 vs 55.39±8.68 g/cm2/s, $p<0.05$). RESUS+VH rats treated with PDTC also exhibited significantly lower STAT-3 activation compared to RESUS+VH rats treated with vehicle (3.58±0.43 vs 4.62±0.39 activity/mg protein, $p<0.05$). In conclusion, NF-kB plays an important role in edema induced intestinal dysfunction which can be attenuated by PDTC.

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INTERNATIONAL MEDICAL STUDENTS

ABSTRACT

Correlation between nitric oxide production and hemodynamic changes during experimental septic shock in conscious rats.

LING GONG *Shanghai Jiao Tong University School of Medicine*

Sponsored by: Marie-Francoise Doursout, Ph.D, Department of Anesthesiology
Supported by: Shanghai Jiao Ton Univeristy School of Medicine
Key Words: Sepsis, nitric oxide, blood pressure, rats

Introduction: Sepsis is a major cause of morbidity and mortality in intensive care. Nitric oxide (NO), an endogenous vasodilator, has been associated with the hypotension and cardiac depression of septic shock. Furthermore, NO is cytotoxic and may cause direct tissue injury and contributes to sepsis-induced multiple organ failure. The goal of this study was to assess the time course of nitrate production associated with hemodynamic changes induced by lipopolyssacharide (LPS)-induced septic shock in conscious and chronically instrumented rats.
Materials and Methods: Under isoflurane anesthesia, rats were instrumented to record arterial mean blood pressure (MAP), heart rate (HR) and cardiac output (CO). Systemic vascular resistance (SVR) was calculated as the ratio MAP/CO. At least 5 days after surgery, animals received LPS at 20 mg/kg IV over 5 min. Hemodynamic parameters (MAP, HR, CO) were recorded at baseline, at the end of LPS, 30 min, 1 hr, 2 hr, 3hr, 4 hr, 6hr and 24 hr following LPS infusion. Simultaneously with hemodynamic measurements, blood samples were collected to further record nitrate production. Data were analyzed using ANOVA for multiple comparisons. Data are expressed as Mean ± SEM. $P<0.05$ was considered significant.
Results: LPS induced a significant decrease in MAP at 1 hr and 2 hr by 41% and 14% respectively. Concomitantly to LPS-induced hemodynamic changes, nitrate increased significantly at 6 hr by 70 % and returned to baseline within 24 hr.
Conclusions: Our data suggest that NO is not involved in the early hemodynamic changes induced by LPS. Therefore, other mediators such as bradykinin, kinins remain to be established in this process. However, NO is likely to be involved in the delayed hemodynamic changes induced by LPS. Thus, the proposed research can lead to the development of newer NOS inhibitors that will be tissue-specific or isoform-specific and thereby will have greater utility as therapeutic agents in septic shock.

ABSTRACT

Co-Morbid Anxiety in Autism Spectrum Disorders

HSIAO-MIN G. HSU *Fu-Jen Catholic University, Taiwan* *Class of 2007*

Sponsored by: Katherine A. Loveland Ph.D., Dept. of Psychiatry and Behavioral Sciences
Supported by: Fu-Jen Catholic University, Taiwan
Key Words: ASD, OCD, repetitive behaviors, stereotyped patterns of behaviors

Autism Spectrum Disorders (ASD) are characterized by impairments in social-emotional skills, communication, and repetitive behaviors. Many persons with ASDs also have symptoms of anxiety, which could be part of an ASD or could represent a co-morbid anxiety disorder, since individuals with ASD and those with OCD both have repetitive or compulsive behaviors. This study had three goals: 1) classifying youth with ASD into those with and without clinically significant symptoms of OCD, 2) determining if those with both ASD and OCD differ in levels of anxiety from those without OCD, and 3) determining if there are group differences in repetitive/stereotyped behaviors. Of 106 children and adolescents with ASD aged 7-18 years, IQ $\geq$ 40, 33 met criteria for OCD and 73 did not. These groups had similar proportions of males and females (over 80% males) and no significant differences in age and IQ. Differences in anxiety were examined using the Conner's Parent Rating Scale-Revised (CPRS-R) and Conner's Teacher Rating Scale Revised (CTRS-R). On the CPRS-R but not the CTRS-R, the ASD-OCD group had significantly higher anxiety and shyness than the ASD-only group ($t(72) = 2.69$, $p = .003$), and more of them met criteria for Specific Phobia ($\chi^2(1) = 18.38$, $p < .001$) and Social Phobia ($\chi^2(1) = 8.18$, $p < .02$). Differences in repetitive/stereotyped behavior were compared using the Autism Diagnostic Interview-Revised (ADI-R). The ASD-OCD group had significantly greater compulsions or rituals ($t(101) = 3.47$, $p = .001$) and difficulties with minor change ($t(98) = 2.97$, $p = .004$). In conclusion, this study identified a subset of individuals with ASD who met criteria for OCD and who also had more anxiety, phobias, compulsions, and difficulties with change. These results suggest there is a significant subgroup of persons with ASD who can be considered to have co-morbid OCD, and that these persons exhibit greater symptoms of anxiety and anxiety disorders more generally.

ABSTRACT

Characterization of the Interaction of the E6 and Net1A Oncogenes with Tumor Suppressor Dlg1 *in vitro*

JUO, HSIN-HSUAN *Fu-Jen Catholic University, Taiwan* *Class of 2010*

Sponsored by: Jeffrey A. Frost, PhD, Department of Integrative Biology and Pharmacology
Supported by: Fu-Jen Catholic University, Taiwan
Key Words: PDZ domain, Net1, Net1A, E6, Dlg1

Rho GTPases of play important roles in many aspects of normal cell physiology and in cancer. They function as molecular switches, cycling between their active, GTP bound and inactive, GDP bound states. The neuroepithelioma transforming gene 1 (Net1) is a RhoA activating protein that also has oncogenic activity. This activity is dependent upon interaction with PDZ domain-containing proteins such as the tumor suppressor discs large 1 (Dlg1). Other oncogenes that interact with Dlg1 include the E6 oncoprotein from the human papilloma virus, which causes nearly all cervical cancers.

The purpose of my project was to characterize the binding of Net1A and E6 with the PDZ domains Dlg1. To do this it was necessary to express and purify recombinant proteins from *E. coli*, and establish an *in vitro* binding assay to measure interaction with the PDZ domains. I first subcloned Net1A into the bacterial expression plasmid pRSETA to enable the production of a hexahistidine tagged version of Net1A. BL21DE3 *E. coli* were separately transformed with this plasmid as well as another for expression of a GST-E6 fusion protein, and the expression of each protein was induced by addition of IPTG. The Net1A was then isolated by nickel-agarose affinity purification, and the E6 was isolated by glutathione-agarose affinity purification. I then characterized the interaction of GST-E6 with purified, recombinant PDZ domains 1-3 from Dlg1 (PDZ 1-3) by GST pulldown assay. Interaction with PDZ1-3 was measured by quantitative Western blotting using antibodies specific for the GST and hexahistidine tags. My analysis included testing the time required for interaction, as well as the concentration dependence for binding. I observed maximal binding of the GST-E6 protein to PDZ1-3 within five minutes at 4^0C, indicating that the GST-E6 protein had a very high affinity for these PDZ domains. I then analyzed the ability of full length Net1A, as well as a peptide corresponding to the PDZ binding site of Net1A, to compete with GST-E6 for binding to PDZ1-3. Preliminary experiments revealed that Net1A was able to compete for binding to PDZ1-3. These experiments indicate that E6 and Net1A bind to the same PDZ domains of Dlg1, and provide a basis for modeling the interaction between Dlg1 and these two oncogenes. In the longer term these results will provide insight into the individual mechanisms for oncogenic transformation by these proteins.

ABSTRACT

FMRI of Working Memory in Cocaine Abuse

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Sponsored by: Joel L. Steinberg, M.D., Department of Psychiatry and Behavioral Sciences
Supported by: F-Jen Catholic University, Taiwan
Key Words: FMRI, working memory, cocaine

The purpose of this study was to determine abnormalities caused by cocaine abuse in brain function during working memory. Functional magnetic resonance imaging (fMRI) scans were acquired from normal controls and cocaine abusers while performing a working memory task, the immediate memory and delayed memory task (IMT/DMT). Philips 3.0 MRI scanner was used with echoplanar pulse sequence. The fMRI time series was processed using slicetime correction, realignment, and coregistration. AFNI software was used to transform time series to Talairach atlas. Results wre analyzed using Statistical Parametric Mapping (SPM) and Statistical non-Parametric Mapping (snpm). Both normals and cocaine users had many areas that showed significant blood oxygenation level dependent (BOLD) activations (spm $p<0.05$ corrected for multiple comparisons) during DMT compared to IMT. Normals had greater activation than cocaine users in the following brain regions during DMT relative to IMT: Superior Temporal and Anterior Cingulate Gyrus. Cocaine subjects had greater BOLD activation than normals in the following regions: Middle Cingulate, Inferior Frontal, and Postcentral Gyrus. These results were statistically significant (SNPM) at the $p<00.05$ cluster level uncorrected for multiple comparisons. In conclusion, the normals activated different areas during working memory tasks than cocaine abusers. These results may be due to effects of cocaine on neuronal circuits.

ABSTRACT

Epstein - Barr virus Genotypes in Multiple Sclerosis

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Sponsored by: John William Lindsey M.D., Department of Neurology
Supported by: Shanghai Jiao Tong University School of Medicine, China
Key Words: multiple sclerosis, Epstein - Barr virus, strains, PCR

Background: Infection with Epstein-Barr virus (EBV) is associated with multiple sclerosis (MS). The relation between the virus infection and the disease is not known. A single study suggests that MS patients may have a different strain of virus than controls [1]. To investigate this relationship, we used sequences from the Latent Membrane Protein-1 (LMP1) gene to determine the strains of virus present in our patients [2,3.] **Materials and methods:** DNA was extracted from mononuclear cells from peripheral blood samples of 29 MS patients and 25 healthy controls. A 619 bp segment of the EBV LMP-1 gene was amplified using nested (two-stage) polymerase chain reaction (PCR) using primers which are located in highly conserved areas. This region has been used for strain identification by others, and includes a variable number of 33 base-pair repeats as well as 15 and 30 bp deletions. **Results:** We amplified and sequenced a product from 10 of 29 MS patients and 6 of 25 control specimens. The detection ratio of 34.5% among patients was not significantly different (*p=0.55)* from the 24% ratio for controls using Fisher's Exact Test with 0.05 alpha. Multiple different sequences were found in both MS and controls. There were some possible differences between the MS and control groups. The number of 33bp repeats tended to be smaller in the MS group with the patient group ranging from 3-5 repeats while controls show 4-6 repeats. 50% of control samples exhibit six 33bp repeats while an equal proportion of MS patients have four repeats. The 30bp deletion, which has been suggested to have oncogenic potential[3], was not found to be significantly different among patient or control genotypes (*p=0.607)*. The 15 bp deletion also didn't differ significantly between the MS group and controls (*p=0.604)*. Phylogenetic analysis using minimum evolution method reveals unique branch which includes three of the ten MS samples and no controls. These sequences share 10 point mutations and have three 33bp repeats. This finding is quite interesting but further study will be required to determine whether this strain is found exclusively in MS. **Conclusion:** Characterization of EBV strains through LMP1 genotype screening reveals several interesting patterns, particularly the presence of one virus strain found only in MS patients. Due to small sample size, this observation needs to be replicated in a larger sample.

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Undergraduates

ABSTRACT

Genomic Screen for TAAD Causing Mutation

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Sponsored by: Dianna Milewicz, MD, PhD, Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: TAAD, mutation, genomic screen, aneurysms, dissections

Thoracic aortic aneurysms and dissections (TAAD) are the most common diseases affecting the human aorta and frequently result in premature death. Familial TAAD is an autosomal dominant disorder demonstrating genetic heterogeneity. Microsatellite genotyping analysis mapped a locus for familial TAAD to 15q, using DNA from affected individuals from three unrelated families each with multiple members diagnosed with TAAD allows for the identification of the defective gene causing TAAD at this locus. My project included the sequencing of two large, unrelated families at the TAAD3 locus in order to identify the defective gene at the 15q critical interval. The genes that I sequenced in the 15q region were MCTP2, PRC1, FES, Furin, and SV2B. Genomic DNA from affected individuals was amplified using intron-based, exon-specific primers and directly sequenced in the sense and anti-sense directions. No disease-causing mutations were identified in these genes. Sequencing of further genes in the region is currently underway. In conclusion, my project excluded 5 genes in the critical interval at the TAAD3 locus at 15q as a cause of familial TAAD.

ABSTRACT

The Interaction Between the N-Terminus of Giα with the C_1 Domain of Type V Adenylyl Cyclase

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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: Adenylyl Cyclase, Giα, cAMP

Adenylyl cyclase converts ATP to cAMP, a second messenger in diverse cellular responses. Giα is a physiological regulator of adenylyl cyclase types I, V, and VI. Myristoylation of Giα enhances the inhibition of adenylyl cyclase. To better understand the interaction sites between the N-terminus of Giα with the C_1 domain of type V adenylyl cyclase, 10 residues were mutated to cysteine within the N-terminus of Giα. Clones 13C and 14C, myristoylated and non-myristoylated, were transformed into BL21 expression host cells. Non-myristoylated proteins were isolated using Ni-NTA columns and myristoylated proteins using Ni-NTA and phenyl sepharose columns. The presence of 13C-NM, 13C-Myr, 14C-NM, and 14C-Myr was confirmed by urea gel electrophoresis and protein concentration was determined using a Bradford assay. G proteins were activated by incubation of Giα with GTPγS and free GTPγS was removed through gel filtration. The concentration of active protein was determined by scintillation counting of [^{35}S] GTPγS bound to Giα. An adenylyl cyclase activity assay was performed in which type V adenylyl cyclase was incubated with 13C-NM and 13C-Myr. Alpha [^{32}P] ATP was added to measure the amount of radioactive cAMP produced, and the amount of inhibition by NM-13C and 13C-Myr Giα proteins. The IC_{50} was determined to be 1 μM Giα, similar to results with wild type Giα, indicating this mutation does not affect the inhibition of type V adenylyl cyclase. Further activity studies will be used to confirm this conclusion and to test the remaining constructs to determine the sites of interaction between Giα with type V adenylyl cyclase.

ABSTRACT

Hypertonic Saline Treatment For Shock-Induced Gut Ischemia

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Sponsored by: Rosemary Kozar, MD, PhD, Department of Surgery
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: ischemia, hypertonic saline, shock

Shock is a frequently diagnosed clinical condition in which there is an acute circulatory insufficiency of the blood to the organ systems. Shock-induced ischemia has been shown to be a major risk factor for multiple organ failure (MOF), and the gut seems to play a pivotal role in the MOF pathogenesis. The current standard of care for resuscitation is isotonic crystalloids (ISO) which serves to rapidly expand plasma volume and replenish extracellular fluid to minimize severity of the ischemic insult. However, during massive resuscitation ISO has been shown to cause problematic edema in the lungs, brain, and gut. In addition, recent studies show that the standard of care is pro-inflammatory which may cause further tissue damage. We believe hypertonic saline (HS) may be a more adequate standard of care because it requires less volume than ISO, prevents red blood cell and endothelial cell swelling, and has been shown to down regulate neutrophils which are believed to increase inflammation and lead to increase tissue damage. To test our hypothesis, the rat superior mesenteric artery occlusion model is used; rats receive 4 cc/kg of HS at 60 minutes post-ischemia. The distal ileum is harvested following 6 hours reperfusion, and samples are assayed for the pro-inflammatory mediators NFKB, AP-1, iNOS, and COX-2 as well as the anti-inflammatory mediators HO-1 and PPAR. Conclusions from this project will lead to more effective prevention and treatment for shock patients, as well as provide further insight into the inflammatory mechanisms of the gastrointestinal track.

ABSTRACT

Visual Timing Recalibration Using See-Thru Virtual Reality Goggles

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Sponsored by: David Eagleman, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: timing, metronome, virtual reality, recalibration

When one snaps their fingers they see, hear and feel the snap simultaneously, even though the sensory feedback is processed at different speeds in the different senses. A previous experiment found that when a delay of 100 ms was injected between a subject's keypress and the resulting visual feedback (a flash of light), the brain recalibrated its perceived timing such that the two events seemed simultaneous. When the delay was then shortened to 40 ms, subjects perceived the flash to come before the motor output. To magnify the behavioral salience of the task, this experiment used a 'see-thru' virtual reality VR headset to analyze recalibration of motor-sensory timing in a total immersion visual feedback experiment. In a 'see-thru' system, a VR headset with two front mounted CCD cameras was used to inject a visual delay of 90, 120, 260 and 480 ms for a 100 second block. Each block was followed by a 'headset-off' block. Subjects preformed a tapping task in which they were asked to match the sight of their tapping finger to a metronome (1 beat/sec). The offset between the sound and the finger tap was analyzed for each block. The current data reflects no obvious trend. Subjects with musical training were more accurate in all conditions than those who had little or no musical training. Tactile feedback was not removed in this experiment, potentially causing confusion between the senses. Further testing should use an input device which allows for clear visual feedback without tactile feedback.

ABSTRACT

L650T Mutation in Neurological Ion Channels

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Sponsored by: Vasanthi Jayaraman, PhD, Department of Integrative Biology and Pharmacology

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

Key Words: Glutamate receptors, AMPA, L650T

In the central nervous system, the major mediators of excitatory synaptic signals are glutamate receptors. They play an important role in learning, memory, and in diverse neuropathologies such as ischemia. Based on the agonist efficacy these receptors are classified into three subtypes: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartic acid (NMDA), and Kainate. Extensive insight has been obtained from the crystal structures of the isolate ligand binding domain of the GluR2 subunit that belongs to the AMPA subtype of the receptor. These results show that the ligand binding domain undergoes cleft closure upon binding agonists and the extent of activation by the agonist correlates well with the extent of cleft closure. The L650T mutation of the GluR2 receptor is however, an exception and does not follow this trend. For instance the AMPA bound form of this mutant protein is much more closed than expected based on its activation. We therefore decided to study this protein to understand the reasons for this deviation. The L650T ligand binding domain was expressed with a N-terminal histidine tag and a thrombin site. The protein was cultured in E-coli and purified using a Ni-Nitrilotriacetic acid column. The histidine tag was removed using thrombin digestion, and an ion exchange SP-Sepharose column was used to purify the protein from the cut His-tags. Future experiments include vibrational spectroscopy, which will be used to study the ligand protein interaction and thus allow us to gain a better understanding of the mechanisms that control activation.

ABSTRACT

Investigation of Splenic Response to Mycobacterial Cord Factor, Trehalose 6,6'-dimycolate, in C5 Deficient and IL-6 Knockout Mice

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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: Mycobacterium Tuberculosis, Trehalose 6,6'-dimycolate (TDM), Spleen, Granuloma, Interleukin 6, Complement C5

Tuberculosis is the leading cause of death by infectious disease worldwide, attributing to 2 million deaths in 2004. Trehalose 6,6'-dimycolate (TDM) is an abundant glycolipid in the cell wall of Mycobacterium Tuberculosis (MTB), capable of eliciting an MTB-like granulomatous response in mouse models. This study characterizes the inflammatory mRNA response to TDM in the spleen; specifically examining roles for Complement C5 and Interleukin 6 (IL-6). Histological examination following TDM administration showed peak splenic activation at day 7 in wild type (C57BL/6J) mice. The C5 deficient mice (B10.D2-H2d H2-T18c Hco/oSnJ;OSN) never formed focal germinal centers, although peak responses were seen at day 4, decreasing within 14 days. IL-6 knockout mice showed overall reduced activation, with limited formation of true germinal centers. Constitutive mRNA levels were lower in the IL-6 knockouts and higher in the C5 deficient mice versus controls. Wild type mice exhibited a graded increase in TNF-α, IL-1 β, and IL-12 mRNA peaking at day 14, while IL-6 increased only at day 14 and IL-10 remained constant. The C5 deficient mice exhibited an increase in TNF-α, IL-1β, and IL-10 signal at day 4, with levels below controls by day 14; IL-12 and IL-6 were down-regulated. IL-6 knockout mice had a rapid increase in TNF-α and IL-1β reaching a maximum at day 4; levels were maintaining through day 14. IL-10 and IL-12 both increased slightly reaching a maximum at day 7. These findings allow us to propose a regulating role for C5 in the initiation of the immune response. In the IL-6 knockouts there seems to be an overall less robust response, which is not maintained. It is theorized that the bioactive role for IL-6 is likely taken over by TNF-α and IL-1 β, but IL-6 is still require for activation of the granulomatous response.

ABSTRACT

Toward a High Resolution 3-D Reconstruction of Rice Dwarf Virus

STEPHEN A. COFFMAN *University of Texas at Austin* *Class of 2007*

Sponsored by: Z. Hong Zhou, Ph.D., Assoc. Prof., Dept. of Pathology and Laboratory Medicine

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

Key Words: reconstruction, structure, rice dwarf virus, cryomicroscopy

Rice dwarf virus (RDV), belonging to the family *Reoviridae*, is a pathogen primarily transmitted by Nephotettix cincticeps leafhoppers leading to systematic infections in rice and wheat crops. Significant economic consequences have resulted from its spread across China and Japan. The RDV structure was recently determined to 3.5-Å resolution by x-ray crystallography using RDV crystals. The availability of this atomic resolution structure makes it an ideal test sample for advancing cryo-electron microscopy (cryoEM) reconstruction to atomic resolution without the use of crystals. The goal of the current study is to optimize and validate single particle cryoEM reconstruction to atomic resolution using RDV as our model system. As a first step toward this goal, I have processed approximately 1800 RDV images using our integrated single particle reconstruction package, called IMIRS (Image Management and Icosahedral Reconstruction System). The far-from-focus images were used to identify the position of the RDV particles and later to reconstruct a map, which is used to refine the parameters of the close-to-focus particles. Averaging and refining the far-from-focus image data generated a 15-Å resolution model using 1453 selected images. Ongoing work will include the processing of more images and the close-to-focus image data using the 15 Å model as a starting template to generate a higher resolution reconstruction. The successful reconstruction of a high resolution model for RDV will validate the method of integrating cryoEM with IMIRS to resolve macromolecular structures at high resolution levels. The method may then be used accurately for high resolution reconstructions of unknown structures of other macromolecular machines.

ABSTRACT

Deletion of Adhesin Genes from the Chromosome of *E. faecalis*

CLAY T. COHEN *Furman University* Class of 2007

Sponsored by: Philip Johnson, MD, Department of Internal Medicine
Robin Hardwicke, PhD, Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Depression, BDI, HIV

A major barrier to successful antiretroviral treatment in HIV positive patients is psychological factors, such as depression. Due to the social stigma that follows an HIV+ diagnosis, many HIV patients are especially vulnerable to mental disorders. As a result of impeding patient compliance to medication, psychological issues hinder the immune system as well as increase the resistance of the virus to antiretroviral therapy. It is also believed that other factors may influence medication compliance, including familiarity with the virus, education level, socioeconomic status, and continuity of care. In order to improve the effectiveness of therapy, physicians need a method to efficiently recognize the initial stages of depression in their patients. A developed two-part questionnaire, the UT-Houston Depression Tool (UT-HD), was used alongside a proven, yet lengthy, survey, Beck's Depression Inventory (BDI), and administered to one hundred HIV+ patients. After a month, the first thirty five patients enrolled completed both surveys again for validity purposes. Through the creation of a scoring method for each tool, the results were analyzed to determine the accuracy of the UT-HD. While the analysis of the data is still pending, it appears that the UT-HD tool was more sensitive in diagnosing depression. Ultimately, however, an efficient diagnostic tool will allow clinicians inexperienced with mental disorders to recognize and treat depression in HIV+ patients; resulting in an improved HIV+ patients; resulting in an improved HIV status and quality of life for patients.

ABSTRACT

Deletion of Adhesin Genes from the Chromosome of *E. faecalis*

MARISSA C. DANIELS *Rice University* Class of 2008

Sponsored by: Barbara E. Murray, MD, Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
U.S. Public Health Service Training Grant T32 AI55449
Key Words: *E. faecalis*, adhesins, deletion mutant

The multi-drug-resistant bacterium *Enterococcus faecalis* is an opportunistic pathogen that causes many serious infections such as endocarditis. Adhesin proteins presumably assist colonization of the host tissue by binding to proteins in the ECM. Previous studies have identified putative adhesins of *E. faecalis* that appear to be expressed during infection in humans, and preliminary data from my mentor's laboratory found that purified EF2505 recombinant protein (expressed in *E. coli*) bound to fibrinogen. The goal of this project is to delete two of these predicted adhesin genes (*ef2505* and *ef1269*) from the chromosome of *E. faecalis,* which we predict will cause a reduction in adherence and virulence. To detect whether the encoded proteins are produced in *E. faecalis* OG1RF under laboratory growth conditions, we initially performed western blots with mutanolysin extracts of wild type strains (OG1RF) that identified single reactive bands of both EF2505 and EF1269 as anticipated, suggesting that these proteins are both produced on the surface of OG1RF. To obtain these deletion mutants, we attempted to use the double crossover recombination method with the PheS counter-selection system using pCJK47. Polymerase chain reaction (PCR) generated the flanking regions of the genes of interest, and based on the overlapping regions that we designed into the internal ends of the flanking regions we then performed crossover PCR and confirmed that the crossover PCR products had joined these regions together to form the deletion construct. Since multiple attempts to clone these crossover PCR products directly into pCJK47 failed, we then cloned these products into the pCR2.1 (TA cloning) vector. Analysis of inserts in the TA vector found unexpected deletions at both ends of the recombinant constructs. The reasons for these deletions are unknown but their occurrence suggests that the constructs - which have active promoters and RBSs - could generate something that is toxic to *E. coli*. Future studies will involve generating different constructs that will not produce the same recombinant products, and once the deletion mutants are confirmed they will be tested for changes in adherence to ECM proteins and eventually in an endocarditis model.

ABSTRACT

Comparison of PCR methods for Site-Directed Mutagenesis of microsomal prostaglandin E Synthase-1 (mPGES-1)

MARY LANDON DOWNS *Rhodes College* *Class of 2008*

Sponsored by: Ke-He Ruan, MD, PhD, Department of Hematology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Polymerase chain reaction (PCR), touchdown PCR, DPN-1 digestion, tyrosine (Y) to phenylalanine (F) mutations

A polymerase chain reaction (PCR) is a technique used to amplify small amounts of DNA exponentially. There are several PCR techniques for mutating DNA. Our goal is to mutate six tyrosine (Y) residues on microsomal prostaglandin E Synthase-1 (mPGES-1) to phenylalanine (F) (Y28F,Y58F, Y80F, Y89F, Y117F, and Y130F). The site specific primers used also introduced HindIII and EcoRI restriction enzyme sites. Three different PCR techniques were used: (1) Three-Step PCR; (2) PCR with Dpn I digestion; (2) and Mismatch Primer Template Pairs in Touchdown PCR. Conventional three-step PCR proved successful for attaching the restriction enzymes but not for making mutations. The next technique examined DpnI digestion. DpnI—an enzyme that digests the methylated (parental) DNA—leaves only the amplified DNA. The DpnI digest technique resulted in Y to F mutations for three samples (Y130F, Y28F, and Y58F), although sequencing results showed the presence substantial wildtype sequence. To get a more homogeneous mutated product, a technique called mismatch primer touchdown PCR (MPT-PCR) was performed. Touchdown PCR involves a series of cycles in which the annealing temperature is incrementally lowered in order to favor the preferential priming of the primer-template combination. Mismatched primers use two mutated PCR products as primers to get a more specific product. The resulting sequences from MPT-PCR showed the desired mutation for Y117F without the presence of contaminating wildtype sequence. These results lead to the conclusion that MPT-PCR is a more effective and efficient method of mutagenesis than conventional or DpnI digest PCR reactions for mPGES-1 mutations.

ABSTRACT

Bond Strength of SnapBond to Enamel and Dentin

MARY B. ELDIWANY *The University of Texas at Austin* Class of 2006

Sponsored by: Joe C. Ontiveros, DDS, MS, Department of Restorative Dentistry and Biomaterials

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

Key Words: Shear bond strength, adhesives, enamel, dentin

Objective: The purpose of this study is to determine the shear bond strength of resin composite to human superficial dentin and enamel using SnapBond dental adhesives compared to a control.

Method/Materials: Extracted teeth were sectioned from their roots, mounted in acrylic resin and wet ground to a 600-grit finish to expose buccal lingual superficial dentin or enamel. Dental adhesives Copalite SnapBond and Prime & Bond NT, the control, were applied to enamel or dentin according to the manufacturer's instructions. The adhesive was cured for 20 seconds once the test specimen was secured in the bonding jig. A cylindrical mold (d=2.3 mm) placed flat against the tooth surface established a standard distance of 4.2 mm from the curing tip to the adhesive for each specimen. The mold was then loaded with resin composite (Z100, shade A2) and cured for 40 seconds using a standard halogen light (Optilux 501). Testing was conducted after storage at 37^{O}C for 24 hours using the Instron at a crosshead speed of 1.0 mm/min. The data was analyzed using ANOVA and Tukey's post hoc at the 0.05 level of significance.

Results: A significant difference in shear bond strength was shown between the two dental adhesives with Prime & Bond showing higher values for enamel ($p<.02$) while SnapBond showing higher values among the dentin groups ($p<.001$). The main effects of substrate showed higher bong strengths among enamel ($p<.001$) while the main effects for adhesives showed no significant difference ($p=.055$).

ABSTRACT

Structural Characterization of the Second and Third Iintracellular Loop of Human Thromboxane A_2 Receptor

MARY K. FENG *The University of Texas Austin* Class of 2009

Sponsored by: Dr. Ke-He Ruan, MD, PhD, Division of Hematology, Department of Internal Medicine

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

Key Words: G protein; TP receptor; intracellular loop

Understanding of the specific details of the coupling between prostanoid receptors and their specific G proteins lies in the structural characterization of their intracellular domains. It has been reported that the multiple intracellular loop (iLP) of thromboxane A_2 receptor (TP) is involved in the receptor G protein coupling. The lack of a 3D structure for the receptor has become a major obstacle in understanding the molecular mechanisms regarding the detailed contacts between the receptor and G protein. In this study, a high-resolution 2D NMR technique was used to determine the 3D structures of the second and third iLPs of the TP receptor using synthetic peptides constrained into the loop structures. After the peptide synthesis and purification, 2D ^{1}H NMR spectra, TOCSY and NOESY for the two peptides were obtained from proton NMR experiments using 600 MHz NMR instrument. The NMR data was processed and assigned through the Felix2000 program. Standard methods were used to acquire peak and sequential assignments. Final calculations and structures were processed through DGII and NMR refinement programs within the Insight II program. We were able to calculate and use the NOE constraints to obtain the superimposition of ten structures for each iLP peptide. The finalization of this project resulted in two configurations of iLP2 and iLP3 with respect to transmembrane 3 and 4 and transmembrane 5 and 6 respectively. These results will support future analysis of the whole intracellular domain for the TP receptor and providing structural information to further characterize the structural and functional relationship of the G protein coupled receptor.

ABSTRACT

Structural Characterization of the Second and Third Iintracellular Loop of Human Thromboxane A_2 Receptor

DANIEL T. FUNG *The University of Texas* *Class of 2008*

Sponsored by: Dr. Ke-He Ruan, MD, PhD, Division of Hematology, Department of Internal Medicine

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

Key Words: Thromoboxane A_2, Thromboxane A_2 synthase, Cyclooxygenase

Thromoboxane A_2 (TXA_2) is a vasoconstricting and proaggregatory mediator which is an important factor leading to thrombosis, stroke and heart attack. Understanding of the molecular mechanisms of the TXA_2 biosynthesis in coupling reaction between TXA_2 synthase (TXAS) with cyclooxygenase (COX) is a key step for the development of new therapeutic interventions against the vascular diseases. In this project, we investigated how the N-terminal membrane anchor domain of the membrane-bound thromboxane synthase affects its substrate presentation in the coupling reaction. We constructed a COX/TXAS coupling reaction system using arachidonic acid (AA) as a substrate in a membrane-bound environment. A chimeric molecule (TXAS-20chi) in which the N-terminal membrane anchor domain of TXAS was replaced with the corresponding 20 residues of PGIS was created. The biosynthesis of TXA_2 by TXAS-20chi in the coupling reaction with COX-1 was significantly decreased in comparison with that of the wild type TXAS in HEK cells which were co-transfected with recombinant COX-1 and TXAS. Furthermore, the chimera revealed a considerable delay in the PGH_2 presentation when AA was used as a substrate in a time-course reactions. These results show that the N-terminal membrane bound region of TXAS is involved in the substrate presentation during the coupling reaction with COX-1 in the membrane-bound environment in the cells.

ABSTRACT

Transposon Mutagenesis of *Borrelia burgdorferi*

JESSICA R. GALLOWAY-PENA Our Lady of the Lake University Class of 2006

Sponsored by: Steven J. Norris Ph.D., Department of Pathology

Supported by: The University of Texas at Houston Medical School - Summer Research Program and
The US Public Health Service/National Institutes of Health Grant entitled "Molecular Basis of Infectious Disease" # T32 AI055449

Key Words: Lyme disease, *Borrelia burgdorferi*, transposon mutagenesis, pMarGent, *Himar1*

Lyme disease is the most prevalent vector-borne disease in North America and Eurasia. The chronic neurological and arthritic symptoms can be devastating if untreated. Extensive studies have been performed with *Borrelia burgdorferi*, the causative agent of Lyme disease in North America. However, there is limited knowledge regarding the genes required for infectivity and pathogenesis of Lyme disease. In this study, the use of transposon mutagenesis to identify the genes necessary for infectivity was examined for practicality and effectiveness. The infectious strain 5A18NP1 was transformed with pMarGent, a *Himar1* transposon delivery vector containing a gentamicin cassette, in order to create a library of random insertion sites in the *B. burgdorferi* genome. After the insertion sites were characterized, single mouse inoculations were performed with 37 unique transposon mutants from the library. Cultures from the bladder, ear, heart, and joint tissue were analyzed in order to determine which mutants were noninfectious and VlsE ELISAs were performed to provide confirmation for the culture results. The non-infectivity of a mutant denotes that the gene containing the insertion site may be involved in pathogenesis. Mutants that are attenuated or noninfectious *in vivo* are currently being identified and will be examined in more detail. This study indicates that random transposon mutagenesis is a practical and effective method for determining pathogenic factors in *B. burgdorferi*. The results also provide insight into the genetics and mechanisms of pathogenesis of Lyme disease, which may eventually lead to better diagnosis, treatment, and prevention.

ABSTRACT

Characterization of the role of Csl4p in Exosome Function

EESHITA GHOSH DASTIDAR *Angelo State University* Class of 2007

Sponsored by: Ambro van Hoof, PhD, Department of Microbiology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Exosome, CsL4, mRNA degradation

The exosome is a protein complex that is involved in mRNA degradation, in processing other RNAs, and in antiviral defense. It contains ten proteins of which seven proteins are putative 3'5' exoribonucleases and the other three proteins are putative RNA binding proteins. A major question regarding the exosome is what the role is of individual subunits for individual functions. It is also intriguing how the exosome differentiates between substrates it degrades and substrates it processes. In this study we focused on the Csl4p subunit, which has an unknown essential function but may also have a special role in mRNA degradation. The Csl4p protein contains three domains, an N-terminal domain, and 51 RNA binding domain and a zinc ribbon domain. In this study we tested whether all three domains were required for the different functions of the Csl4p subunit of the exosome by creating mutations in the yeast CSL4 gene.

ABSTRACT

Voxel-based Morphometry: Whole Brain Segmentation Protocol Design and Application for the Adolescent Brain.

CHRISTOPHER R. HALPHEN *Louisiana State University* Class of 2006

Sponsored by: Khader M. Hasan, PhD, Department of Diagnostic and Interventional Imaging
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: VBM, segmentation, MRI

Magnetic resonance images can vary in numerous ways from subject to subject. This adds obstacles when trying to locate trends in pathology and aging amongst a study group. A measure of structural difference amid populations is calculated from the assessment of the composition of different brain tissues (grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF)). Voxel-based morphometry (VBM), based on the Gaussian theory, normalizes data and smoothes peak intensities for a more ornate image. There are many programs and algorithms designed to optimize this approach of segmentation in adults; however, few are optimized for children. From extensive research of published literature and application of protocols, an optimized approach was formulated. Using a MATLab application (SPM2), VBM segmentation of the adolescent brain can be accurately estimated after the design of a study specific child template. For this study, dual echo data (proton density-weighted (PDw), and spin-spin relaxation-weighted (T2w)) was examined for its contrast obtained in a single scan reducing the risk of inconsistencies during scanning. A PDw template was molded from pediatric control data (age 6-18yrs) from ongoing studies after co-registration and normalization. This protocol was compared with results from other standardized methods and a diffusion tensor segmentation method designed in the DTI lab. Along with crisp images, approximately a 2:1 ratio of GM to WM and comparable CSF was found. This study has opened many doors for analyzing fast developing brains of children through aging and pathological disorders with a window for a more region of interest based approach.

ABSTRACT

Comparison of Cognitive and Behavioral Function in Children with an ASD With/Without ADHD

STEPHANIE A. HANSON *Yale University* Class of 2007

Sponsored by: Deborah A. Pearson, Ph. D., Dept. of Psychiatry and Behavioral Sciences
Supported by: The Univ. of Texas at Houston Medical School - Summer Research Program
Key Words: ADHD, ASD, response inhibition, impulsivity

Many children with autistic spectrum disorders (ASD) also have symptoms of Attention Deficit Hyperactivity Disorder (ADHD). However, at this point, little is known about how the cognitive and behavioral symptoms of ADHD (e.g., disinhibition) are manifested in children with ASD's. Thus, one of the overall goals of our project is to compare cognitive and behavioral functioning in: 1) children with an ASD who also have clinically significant symptoms of ADHD, and 2) children with an ASD who do not have significant ADHD symptomatology.

Although inhibitory control deficits are one of the major impairments associated with ADHD in the general school-age population, little is known about inhibition in children with ASD who also have symptoms of ADHD. Within this population, it is also unknown if more severe symptoms of autism are associated with greater inhibitory deficits. To investigate this relationship between inhibition and autistic symptomatology, we compared inhibitory functioning and severity of autistic symptoms in 5 children who had an ASD and also had clinically significant symptoms of ADHD. Inhibitory control was assessed on the Stop Signal Task (SST) by calculating a Stop Signal Reaction Time (SSRT) , which is the theoretical time it takes for a child to stop (or inhibit) making a response they have been instructed to make. Severity of autistic symptomatology was assessed using the Social Communication Questionnaire (SCQ), a parent questionnaire.

Correlations between SCQ scores and SSRTs suggest that children with more severe symptoms of autism also had longer SSRTs--and thus greater impairments in inhibition (r = -0.972, p=0.005). Although these results suggest that children with more severe autistic symptomatology also have greater deficits in inhibitory control, more investigation is needed to examine the nature of inhibitory functioning in children with autism and symptoms of ADHD.

ABSTRACT

Silica Activates Cultured SSc Fibroblasts to Resemble a SSc Phenotype

STEPHEN A. HARDING *The University of Texas* Class of 2009

Sponsored by: Frank C. Arnett, MD – Division of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Scleroderma, Systemic Sclerosis, Silica, Collagen

Systemic sclerosis (SSc) is a multisystem disease in which the primary feature is skin and organ thickening (fibrosis). While the etiopathogenesis of SSc has not been determined, genetic and environmental factors are believed to be the main contributors. Silica has been identified as a putative environmental trigger of SSc. The fibroblasts of SSc skin cells demonstrate a fibrotic phenotype, caused by overexpression of proteins (collagen, CTGF, SPARC) in the extracellular matrix (ECM). Three pairs of SSc patients/controls were matched by sex, age, and race and skin fibroblasts were cultured. Half were untreated and half treated with silica (10 ug). These were grown over 5 days, a sample frozen at each interval. Real-time RT-PCR was used to determine gene expression in controls versus patients. Western blots were used to determine protein expressions, and immunostaining determined the presence of phosphorylated (p) SMAD3. Finally, an ELISA determined the concentration of TGFβ in culture media. Based on RT-PCR, silica-treated control cells showed little change, while expression of ECM genes in SSc cells was increased. In those SSc cells stimulated with silica versus those unstimulated, col1 expression increased 21.28 times (p-value 0.1088), col3 expression 6.16 times (p-value 0.1088), CTGF 1.87 times (p-value 0.2850), SPARC 3.94 times (p-value 0.1088), and TIMP3 1.84 times (p-value 0.2850). From these preliminary data, silica was shown to stimulate SSc fibroblasts in culture. These changes are more pronounced in SSc fibroblasts (i.e. they are more sensitive to silica) than normal controls, and appear to reflect activation of TGFβ signaling pathways.

ABSTRACT

A Model to Evaluate Emergency Victim Decontamination Methods

ESTER N. HUFF *University of Texas at Arllington* Class of 2008

Sponsored by: Richard N. Bradley, MD, Department of Emergency Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Decontamination-methods, emergency treatment methods

Purpose: Many first responders plan to perform drenching water decontamination to victims contaminated by hazardous substances before removing their contaminated clothing. We examined the possibility that this approach may actually increase skin contamination. Methodology: We experimented with various preparations of a non-toxic contamination simulant, Glow in the Dark Pigment (Risk Reactor, Huntington Beach, Calif.), until we found a reproducible model that reliably stained the surface of a hospital scrub shirt but did not cause significant soak-through and skin contamination. After developing the model, we applied the pigment to the subjects following our model. We confirmed the amount of skin contamination with a UV light. We then decontaminated subjects using a shower until their clothing was thoroughly saturated and evaluated the amount of contamination left on the clothing and on the skin using UV light. Results: The optimal contamination model used % tsp of pigment and 15 milliliters of tap water. The resulted in a suspension that we applied to a scrub shirt by fingertip while an experimental subject wore the shirt. We performed four tests of our model. In every case, pigment was left on the clothing even after decontamination. Additionally, there was significant pigment deposition of the skin. This staining involved not only the skin under the shirt, but also contamination of the lower extremities. Conclusion: It may be unsafe to drench asymptomatic people who have been contaminated with a hazardous substance before removing their clothes. We have developed a model that investigators may use for further experimentation.

ABSTRACT

Infectious Diseases in Renal Transplant Patients Receiving Rapamycin Immuno Suppression

SAM E. KIRKENDALL *Texas A&M University* Class of 2007

Sponsored by: Philip C. Johnson, MD, Professor and Director, Division of General Medicine, Department of Internal Medicine,

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

Key Words: rapamycin, immunosuppressant, infection,

Rapamycin (rapa) is a new immunosuppressant to treat renal transplant recipients. We studied 363 renal transplant patients treated primarily with rapa to determine the number, cause, and time frame of infectious diseases. Subjects were studied between November, 1993, and June, 2002. Of 363 patients, 118 (33%) suffered urinary tract infections (UTI's); 22 (6%) had pyelonephritis. 146 cases occurred at a mean of 332 days post transplant; 20 (14%) of the cases occurred between 0-14 days, 45 (31%) between 14-120 days, 42 (29%) between 120-365 days, and 39 (26%) 365 days or later. There was no difference in the mean days post transplant between pyelonephritis or UTI's. Of the urinary infections in which an organism was isolated, 44 (86%) were bacterial, 7 (14%) were fungal. Among 11 pyelonephritis cases, 6 different organisms were isolated. Enterococcus was found in 4 (37%) cases, *E. coli* and *K. pneumonia* were each found in 2 (18%) cases, and MRSA, *P. a*eruginosa, and *C. albicans* were each found in 1 (9%) case. There were 115 respiratory infections among 95 (26%) of the patients; most had pneumonia. These occurred a mean of 624 days post transplant. Of these, 9 (8%) occurred within the first 14 days, 21 (18%) took place from 14-120 days, 19 (17%) were between 120-365 days, and the remaining 66 (57%) occurred over 365 days post transplant. Of the respiratory cases, there were 17 with identified pathogens; 12 (71%) were bacterial, 5 (29%) were fungal, and none had PCP. CMV infections occurred in 29 (8%) of the patients. These occurred a mean of 324 days post transplant. Of these, 1 (4%) occurred within the first 14 days, 13 (45%) took place from 14-120 days, 10 (34%) were between 120-365 days, and the remaining 5 (17%) occurred over 365 days post transplant There were a total of 131 wound infections in 87 (24%) patients. In 39 (30%) there was a pathogen identified. Of these, 35 (90%) were bacterial and 4 (10%) were fungal. Of 363 patients, 12 (3%) died as a result of infections post transplant. We conclude that rapa treated renal transplant patients have more wound infections and less CMV than expected. Resistant bacterial pathogens and fungal infections were more common than previously.

ABSTRACT

Improving Spatial and Temporal Measurement Resolution of Brain Activity by Combining fMRI and MEG

NEEL N. KISHAN *Rice University* *Class of 2007*

Sponsored by: Michael S. Beauchamp, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: fMRI; MEG; surface model

Functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) are two non-invasive methods that measure brain activity using two physically different signals. While fMRI offers spatial resolution on the order of millimeters, it has a poorer temporal resolution compared to MEG, which has temporal resolution on the order of milliseconds. Here we examined how the two techniques can be combined to offer detailed information about brain activity in the spatial and temporal domains.

Tactile stimulation of the left and right hands, feet and face were used for both techniques. Three T1-weighted MRI scans at 3 Tesla were collected from the subject and averaged. The MEG data was aligned to the MRI scans on a cortical surface model which provided a common reference frame. The majority of dipoles were located in primary and secondary somatosensory cortex. Dipoles of the hand stimulations mapped onto the surface showed significantly higher fMRI activation for the same stimulation versus the other stimulations, indicating a high correlation between MEG dipoles and the more spatially specific fMRI activity. Furthermore MEG dipole latencies indicated that activity moved from primary somatosensory cortex (n = 25, mean latency = 47.9±17.9 msec) to secondary somatosensory cortex (n = 8, mean latency = 183±5 msec), indicating a higher level of temporal specificity than the fMRI data.

ABSTRACT

Parvalbumin-Containing Amacrine Cells of the Monkey Retina

KATHRYN E. KLUMP *Oral Roberts University* *Class of 2008*

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 amacrine cells containing the calcium binding protein parvalbumin (PV) in the primate retina. Retinas from 10 monkeys were labeled with antibodies against PV and other neuronal cell markers. These PV-IR cells were examined using confocal and fluoresence microscopy to describe their morphology, neurotransmitter content and interactions with other retinal neurons. The PV-IR amacrine cells have ovoid perikarya in the lower row of the inner nuclear layer, approximately 8 µm in diameter on the short axis and 10 µm on the long axis. The perikarya are separated by approximately 20 µm in mid-peripheral retina, and therefore they are among the most common amacrine cells in the primate retina. The PV-IR cell contains glyt-1, a glycine transporter, and therefore uses glycine as its neurotransmitter. The PV-IR dendrites are thin and overlap, forming a dense plexus extending from the upper border of the inner plexiform layer to approximately 80% of the distance to the ganglion cell layer. Numerous large, spherical varicosities (average diameter 2.5 µm) were observed along the dendrites. These varicosities were the sites of interactions between the PV-IR amacrine cell and lobular dendrites of calretinin-IR, AII amacrine cells. Previous EM studies showed that AII amacrine cells receive synapses from amacrine cells there, and taken together, these results indicate that the PV-IR amacrine cell is presynaptic to the AII amacrine cells. This finding suggest that PV-IR amacrine cells contribute to the processing of signals in the rod pathway.

ABSTRACT

Splenic Response to Cord Ffactor Trehalose 6,6-dimycolate (TDM) in C5 Deficient and IL-6 Knockout Mice

DAVID KUSIN *Yeshiva University* *Class of 2009*

Sponsored by: Jeffrey K. Actor, PhD, Department of Pathology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Mycobacterium Tuberculosis, Trehalose 6'6-dimycolate, TDM, Spleen, Granuloma, Interleukin 6, Complement C5

Nearly one-third of the world's population is infected with *Mycobacterium tuberculosis*, with infection to new individuals occurring every second. The hallmark of disease is the granulomatous response. The mycobacterial surface glycolipid, trehalose-6,6'-dimycolate, also known as TDM or cord factor, has been shown to elicit granulomas that mimic those seen in infection with *Mycobacterium tuberculosis*. Specifically, TDM-induced granuloma formation is a useful model to study pro-inflammatory cytokine production by macrophages and T cells involved in the induction of infectious pathology. The goal of this study was to examine mRNA responses in the spleen following administration of TDM, and to evaluate contributions of complement C5 and IL-6 to cellular activation. Control C57BL/6 mice, C5 deficient (B10.D2-H2d H2-T18c Hco/oSnJ;OSN) or IL-6 knockout mice were evaluated for histological changes. Wild type mice showed splenic peak activation at day 7. Of interest, C5 deficient mice never exhibited focal germinal centers, although inflammatory responses were seen at day 4. The IL-6 knockout mice showed overall reduced activity, albeit with limited true germinal center formation. Following TDM administration, the C57BL/6 mice demonstrated increases in TNF-α, IL-1 β, and IL-12 mRNA through day 14; IL-6 increased only at day 14. The C5 deficient mice exhibited an increase in TNF-α, IL-1β, and IL-10 mRNAs by day 4, but diminished IL-12 and IL-6 by the study's end. IL-6 knockout mice showed rapid upregulation of TNF-α and IL-1β by day 4; while IL-10 and IL-12 mRNA increased only slightly through day 7. These findings indicate a regulating role for C5 in initiation of the immune response. The less robust response in IL-6 knockout mice indicate that there may be compensatory mechanisms in IL-6's absence, however, IL-6 is still required for true granuloma response to TDM.

ABSTRACT

Reaction mechanism of endothelial nitric oxide synthase

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Sponsored by: Ah-Lim Tsai, PhD, Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: nitric oxide synthase

Endothelial nitric-oxide synthase (eNOS) oxidizes L-arginine to L-citrulline and nitric oxide (NO), a major compound causing vasodilation. NOS is the only flavoheme enzyme using tetrahydrobiopterin (BH_4) as a cofactor to reduce the NOS heme-dioxygen intermediate, leaving a BH_4 radical. The mechanism by which the radical is reduced back to BH_4 is still unclear. Two methods are utilized to better understand BH_4 radical recycling and redox communication between the two major eNOS domains. The more direct approach is to truncate eNOS at residue 715 to yield a FMN-heme subdomain. His-tagged FMN-heme domain has been successfully over-expressed in *E. coli*. The alternative approach is to prepare site-specific eNOS mutant(s) crippling the FAD binding site, while minimally affecting protein folding. Preparation of the full-length construct incorporates PCR amplification of wild type cDNA and sub-cloning in TA vector followed by PCW vector. DNA sequencing is used to verify successful cDNA cloning. Once the construct is complete, specific amino acids that interact with FAD will be our targets of mutagenesis. Both full-length and truncated eNOS proteins are overexpressed in BL21 *E. coli* cells, purified using nickel column chromatography, characterized by protein determination, purity checked by PAGE, Western blot and A_{280}/A_{400} ratio, heme analysis by pyridine hemochrome assay, and HPLC analysis for flavin and biopterin. The well characterized proteins will be used for stopped-flow, rapid-freeze EPR and other kinetic measurements to help resolve the mechanisms in question. Supported by NIH RO1 grant: GM56818.

ABSTRACT

Enteric Pathogens in Desserts of Popular Restaurants in Guadalajara, Mexico, and Houston, Texas

ERIC M. LEFEBVRE *Washington University in St. Louis* *Class of 2008*

Sponsored by: Herbert L. DuPont, MD, CID, University of Texas, School of Public Health
Steven J. Norris, PhD, Department of Pathology and Laboratory Medicine
Supported by: Molecular Basis of Infectious Disease Training Grant (T32 AI055449)
Key Words: Mexico, Food, Desserts, Travelers' Diarrhea

Previous studies have shown that travelers' diarrhea is caused by ingestion of food contaminated by bacterial pathogens in high-risk regions. A recent study carried out by our team demonstrated that hot sauces from Mexico were commonly contaminated with fecal coliforms and diarrhea-producing Escherichia coli, known to be important as causative agents in travelers' diarrhea. The summer of 2006 Eric LeFebvre is working to study the potential for desserts from popular restaurants to be contaminated with fecal coliforms and enteric bacterial pathogens. It is hypothesized that the high sugar levels of non-creamed filled desserts with their high osmolarity will be associated with lower levels of contamination compared with other foods previously studied but that contamination levels will be higher in Mexico than the U.S. Approximately 70 desserts from different restaurants in Guadalajara and an equal number in Houston will be sampled and characterized according to: name and type of restaurant, temperature of the dessert and class of dessert (containing cream, ice cream, other). Samples are being collected Sundays through Thursdays at the various restaurants and placed in a thermos containing wet ice immediately after collection and transported to our local laboratory in Guadalajara and Houston for processing the next morning. The variables to compare by food type, temperature and geographic settings will be compared by total coliform counts and presence or absence of specific bacterial enteropathogens. These data will be analyzed and it is anticipated that results will be published in a medical journal.

ABSTRACT

Eye Movements as Behavioral Responses in fMRI Studies of Stroke

ALLISON MACKEY *Queen's University* *Class of 2007*

Sponsored by: Michael Beauchamp, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: eye-tracking, fMRI. somatosensory cortex

Behavioral responses from human subjects during functional magnetic resonance imaging (fMRI) studies are usually collected with button-response devices. However, this presents a problem in fMRI studies of the somatosensory system because of the tactile feedback from the button-press. As an alternative method for collecting responses, we recorded subject eye movements in the MR scanner using a commercial system.
Our participant was a stroke patient who reported somatosensory sensations on the skin of her left arm after hearing sounds. The fMRI experiment consisted of 52 trials of auditory stimuli. Within each trial, we delivered an auditory stimulus (6 seconds) and then presented two visual selection screens (4 seconds each). The patient responded to each screen by making an eye movement to the word that best described her sensation. The first screen described the location of the sensation (None, Hand, Forearm, or Whole arm) and the second screen described its strength (None, Weak, Medium, or Strong). We placed the four words in separate quadrants of the screen to maximize eye position separation. The results from automated eye-tracking were compared with manually viewing the eye image and deciding on the direction of gaze. For 81.7% (85/104) of the responses, both methods gave the same result. The automated eye tracker was unable to determine the response for the remaining trials, because it could not find the pupil (7/19) or the eye position was inaccurate (12/19). Automated eye-tracking is a reasonably accurate method for recording behavioral responses in fMRI studies.

ABSTRACT

Structural Studies of Cytoplasmic Polyhedrosis Virus

MARILYN S. MEZA *Columbia University* *Class of 2009*

Sponsored by: Z. H. Zhou, PhD, Department of Pathology & Laboratory Medicine
Xue-Kui Yu, PhD, Department of Pathology & Laboratory Medicine

Supported by: The University of Texas at HSC Summer Research Program
Molecular Basis of Infectious Disease Training Grant (T32 AI055449, PI: Dr. S. Norris)

Key Words: cytoplasmic polyhedrosis virus, cypovirus, structure

In comparison to other viruses in the family *Reoviridae*, the cypoviruses, such as the cytoplasmic polyhedrosis virus (CPV), are single-shelled. Other dsRNA viruses, exemplified by the rice dwarf virus and the animal reovirus, are typically double- or triple-shelled. Yet, CPV is known to be extraordinarily stable and shares the characteristic endogenous RNA transcription that is common among dsRNA viruses. Thus CPV provides the simplest system for understanding the structural basis of viral RNA transcription and processing. The current study aims to improve the three-dimensional (3D) structure of CPV to near atomic resolution by high-resolution cryo-electron microscopy (cryoEM) and image processing. Higher resolution cryoEM images were recorded with a 16 megapixel CCD camera in a state-of-the-art 300kV cryo-electron microscope (Tecnai Polara from FEI Co.). My work focused on the image pre-processing step using the latest integrated 3D reconstruction package of IMIRS. I have processed a total of 655 pairs of far-from-focus and their corresponding close-to-focus micrograph files. Each micrograph image required manually indicating the focal point of each CPV particle in the thousands of images. The defocus values of the recorded focal pairs are determined by fitting with theoretical curves of the contrast transfer functions. A 3D reconstruction was further generated using the particle images to subnanometer resolution. As data sets continue being collected and processed, they are accumulated to produce an increasingly higher resolution structural model. We are hopeful that a near-atomic resolution reconstruction of the CPV from this ongoing study will help in deciphering the mechanism of the extraordinary capsid stability and the structural basis of endogenous viral RNA transcription.

ABSTRACT

An Investigation of Autophagy in Thermochemotherapy

MICHELLE J. MOLLER *Rice University* *Class of 2008*

Sponsored by: Joan M.C. Bull, MD, Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Autophagy, oxaliplatin, hyperthermia

Thermal therapy is used in combination with chemotherapy to treat aggressive, resistant cancer. Thermal therapy combined with oxaliplatin (Eloxatin) has been shown in vivo to both reduce tumor size directly after treatment but also to stimulate an immune response that results in 50% cure of primary and metastatic tumor in rats. Our laboratory has hypothesized that autophagic cell death, versus apoptotic cell death is responsible for the antitumor response. Autophagy increases the amount of cytosolic protein presented to the MHC Class II molecule, which may stimulate an immune response.

To determine if oxaliplatin combined with thermal therapy significantly increases levels of autophagy in cancer cells, an acridine orange flow cytometry assay was used to detect acidic vacuole organelle (AVO) levels. MTLn3 cancer cells, a highly metastatic rat mammary adenocarcinoma, were cultured in two sets of three increasing oxaliplatin doses (0, .2, and .4 mg/mL): one in 37ºC (normal body temperature) and 40ºC (clinical hyperthermia temperature). While AVO levels were not invariably higher in the 40ºC sets than in 37ºC, the 40ºC sets displayed higher rates of AVO level increase as concentration levels increased, with slope values in 40 ºC 33%, 56%, and 66% larger than in 37 ºC. Hyperthermia seems to enhance the effect of added amounts of oxaliplatin in stimulating autophagy.

To confirm these findings, a preliminary Western blot was performed, detecting MAP-LC3 II, a protein that localizes to the membranes of autophagosomes. First results were inconclusive. Further Western blot autophagy detection assays should be performed to confirm that thermal therapy in combination with oxaliplatin induces higher levels of autophagy than drug alone.

ABSTRACT

The Effect of Attention on Exposure Learning

ALYSSA MORGAN *Trinity University* *Class of 2007*

Sponsored by: Valentin Dragoi, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Attention, exposure, orientaito discrimination, perceptual learning

It is increasingly being understood that the brain adapts to the environment by dynamically changing its sensitivity to relevant incoming stimuli. For instance, the ability of sensory systems to discriminate between nearby stimuli can be improved through repeated exposure or training. It is well accepted that this type of perceptual learning involves a combination of practice-based improvement in behavioral performance and passive adaptation to the exposed stimuli. It has been recently shown (Iliescu et al., 2006) that passive exposure to oriented stimulus sequences induces learning that is stronger than practice-based learning. However, the role of attention in exposure learning has yet to be examined. Here we report that perceptual learning following repetitive exposure to oriented sequences improves more rapidly with attention, whereas unattended, but similar, exposure stimuli lead to inferior learning. We found that daily exposure to series of orthogonal orientations led to an orientation-specific improvement in orientation discrimination. However, human subjects showed a greater improvement in orientation discrimination (along the exposed axes) when attention was directed toward the exposed stimuli relative to the case when the exposure stimuli were unattended. Our study concludes that repeated exposure to incoming stimuli finely tunes the brain along the exposed axes, but the strength of tuning significantly depends on attention.

ABSTRACT

A Study of Cariogenic Oral Microbial Load in Irradiated Head and Neck Cancer Patients

THERESA M. MULLAN *Mercyhurst College* *Class of 2007*

Sponsored by: Millicent C. Goldschmidt, PhD, Professor, Department of Microbiology and Molecular Genetics
Rhonda F. Jacob, D.D.S., M.S., Professor, Maxillofacial Prosthetics Section of Oncologic Dentistry and Prosthodontics, Dept. Head and Neck Surgery

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

Key Words: Xerostomia, Streptococcus mutans, Lactobacillus species, Actinomyces species, chlorohexadine, dental caries, head and neck tumor irradiation

Xerostomia is often a common side effect of radiation therapy in patients with head and neck tumors. Radiation therapy remains the most common treatment for these types of cancers and is difficult to perform without destroying the major salivary glands. This results in an overall decrease in natural oral buffering capacity, including increased oral discomfort, dental caries, and difficulty speaking in and swallowing. Therefore, plaque formation occurs at an increased rate and serves as a reservoir for the development of dental caries and oral decay. The purpose of this preliminary study will be a comparison of the microbial counts obtained from the collection of plaque by flossing with those obtained in a less invasive oral rinse ("swish"). These data are needed prior to testing the efficacy of chlorhexadine as an oral antimicrobial agent. The study consists of twenty irradiated patients treated within the past three months for head or neck tumors, with recent documentation of dental caries, having twenty or more remaining teeth, and having taken no prior antibiotics for four weeks. Patient specimens were suitably diluted in peptone buffered saline and plated on different selective media in an attempt to quantify colony forming units (CFU) of three species of oral flora commonly involved in root and surface caries. Mitis-Salivarius (Difco) medium with bacitracin was used to isolate *Streptococcus mutan*s, Rogossa medium (Difco) was used for *Lactobacillus species*, while specialized PRAS CFAT medium (Anaerobe Systems, Morgan Hill, CA) isolated *Actinomyces species*. Samples were plated in duplicate and incubated for 24 hours anaerobically at 35C. Plates were then incubated aerobically for an additional 24 hours at room temperature. Colony forming units per milliliter of sample were determined by counting in a New Brunswick Quebec colony counter model C-110.

Data was obtained from fifteen patients, including fourty-five total floss and fourty-one total rinse samples. The number and percent of organisms found at and above 1×10^5 CFU (LOG 5) were used as a standard in predicting the best sampling method for future experimentation. The results are reported as LOG conversions from colony forming units (CFU).

A SWISH SAMPLES: 1. *Streptococcus mutans*: six of fourteen were positive (42%) with a range of 5.1 to 6.3, six samples were under five, and two did not grow. 2. *Actinomyces species*: ranged from 6.1 to 7.4 (100%). 3. *Lactobacillus species*: thirteen positive at 5.5 to 7.2 (93%), one at 4.8.

B FLOSS SAMPLES: 1.*Streptococcus mutans*: nine of fifteen were 5.1 to 7.3 (60%), four had no growth, and two were under five. 2. *Actinomyces species*: 5.3 to 7.9 (100%). 3. *Lactobacillus species*: 5.9 to 7.9 (100%). We compared log values rinse to floss for each patient. Consistently higher floss LOG values were found in eight of ten patients for *Streptococcus mutans*, eight of ten patients for *Actinomyces species*, and all patients for *Lactobacillus species*. In conclusion, interpretation of the results further suggests that oral floss is the best sampling method for determining levels of the three oral cariogenic organisms.

ABSTRACT

Diffusion Tensor Imaging of the Corpus Collosum in Developing Healthy Children

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Sponsored by: Khader Hasan, PhD, Department of Diagnostic and Interventional Imaging
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Diffusion Tensor, MRI, Pediatric, Development, Corpus Callosum

Diffusion Tensor Imaging (DTI) provides objective quantitative metrics to study white matter regions in the brain. In particular, the human corpus callosum (CC) can be used as a sensitive marker of the brain's development and its interplay with pathology. DTI was used to study the changes in the corpora callosa of 29 pediatric controls (6-18 years). The callosal midsagittal cross-sectional area (mm^2), mean diffusivity (MD), fractional anisotropy (FA), and tensor eigenvalues ($\lambda_{\parallel}$, and $\lambda_{\perp}$) were calculated using an automated and manual region of interest methods. The Witleson technique was used to divide the CC into its seven functionally specific segments. A MATLab program was written that performed statistical analysis on the data. Statistical analyses on age matched males (N=14) and females (N=15) was also conducted to investigate gender related micro and macro structural differences. Correlation analysis was performed between the FA, MD, $\lambda_{\parallel}$, and $\lambda_{\perp}$ of seven structures of the CC along with age. The program also performed ANOVA analysis on grey matter and CSF for quality control purposes. Our results indicate (a) that the total, subregional, and DTI metrics are not significantly different in the CC of age-matched developing male and female children ($p > 0.3$), (b) FA grows fastest in the CC's posterior and anterior midbody, and (c) the strongest correlation of DTI-based area was found in anterior and posterior midbody and isthmus of the CC. Our findings on the regional callosal growth rates are consistent with previous MRI reports. These findings on pediatric controls helps lay the ground work for further studies of children with specific pathologies and neurodevelopment conditions.

ABSTRACT

The MdgS Protease is a Regulator of *Myxococcus Xanthus 4445* Developmental Gene Expression

MOSES OSORO *The University of Houston - DT* *Class of 2007*

Sponsored by: Heidi Kaplan, PhD, Department of Microbioliogy and Molecular Genetics
Supported by: The University of Texas at Housto Medicla School – Summer Research Program
Molecular Basis of Infectious Diseases Training Grant (T32 A I055449)
Key Words: Envelope stress, signal transduction, microbial development, gene expression

Myxococcus xanthus is a Gram-negative soil bacterium that undergoes multicellular development upon starvation at high density. Expression of the *4445* gene begins 2 hr after the initiation of development, requires starvation and high density, and is controlled by the EcfAiResA/ReaB signaling pathway. This pathway is analogous to the *E. coli* SigE/RseA/RseB signaling system that is activated by certain envelope stresses through the degradation of the RseA anti-sigma factor by the DegS protease. To test if *4445* gene expression is controlled in a similar way, a *M. xanthus degS* homologue, *mdgS,* was identified, mutated and its effect on *4445* expression was tested. If MdgS acts by a mechanism similar to that of *E. coli,* an envelope stress signal (predicted to be a muropeptide released by the cell wall damage) would bind to its PDZ domain activating its trypsin-like protease and eventually permit *4445* transcription. The *mdgS* gene was mutagized by electroporating into *M. xanthus a* Kan^R pBGS18 vector containing an internal fragment of *mdgS.* The *mdgS* mutants, which contain *4445-lacZ* and two mutated copies of *mdgS* separated by vector sequences, were selected by growth on nutrient plates containing kanamycin and were overlaid with X-gal, the chromogenic substrate for β-galactosidase. The *mdgS* mutant colonies were Lac (tan) indicating that they were unable to transduce the inducing signal so that the *4445* reporter gene was not expressed. Expression of *4445* in the *mdgS* mutant was quantitated by an *in-vitro* β-galactosidase assay, which confirmed that MdgS was a regulator of *4445* expression.

ABSTRACT

Isolation of *Bacillus anthracis* Mutants Altered for Protective Antigen and Lethal Factor Synthesis

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Sponsored by: Theresa M. Koehler, PhD, Department of Microbiology and Molecular Genetics
Supported by: U.S. Public Health Service Training Grant T32 AI55449, "Molecular Basis of Infectious Diseases"
Key Words: *Bacillus anthracis*, protective antigen, lethal factor, transposon

The toxin proteins secreted by *Bacillus anthracis* are protective antigen (PA), lethal factor (LF), and edema factor. The structural genes for the proteins are at different loci on the pXO1 plasmid. Regulatory genes for toxin gene expression have been found on pXO1 and the *B. anthracis* chromosome, but data indicate that additional regulators may be present in the genome. In previous work, a *Himar* insertion library was screened by immunoassay for mutants altered for toxin synthesis. One mutant has lost the ability to produce LF and PA. DNA corresponding to a *Himar* insertion site in the mutant was cloned and sequenced. The data indicated that the insertion disrupted the *grpE* gene, predicted to encode a nucleotide exchange factor for the DnaJ and DnaK chaperone pair. Yet, creation of a *grpE*-null mutation in the parent strain did not result in a toxin-deficient phenotype. We hypothesized that the PA- LF- *Himar* insertion mutant carried a second mutation associated with the phenotype. To test this hypothesis, I transduced the *Himar* insertion(s) from the mutant to the parent strain, selecting for the antibiotic-resistance associated with the transposon. I screened six transductants for PA and LF synthesis using Western hybridization analysis. Five transductants were PA/LF-negative and one transductant was PA/LF-positive. These results indicate that the mutant harbors a *Himar* insertion that is directly associated with the toxin-negative phenotype. DNA was purified from the toxin-negative mutant in order to map the specific insertion site.

ABSTRACT

Examination of Gene Pathways in Peripheral Blood Cells of Patients with Systemic Sclerosis

CAMERON POAGE *The University of Texas* *Class of 2008*

Sponsored by: Frank C Arnett, MD, Department of Internal Medicine
Supported by: University of Texas at Houston Medical School - Summer Research Program
Key Words: Systemic sclerosis, peripheral blood cells, microarray

Objective: Scleroderma or systemic sclerosis (SSc) is a clinically heterogeneous disease believed to be of autoimmune origin. Patient with this disease produce one of several mutually exclusive autoantibodies, such as anti- centromere, topoisomerase-I, RNA polymerase III, or others. The objective of this study was to gain a better understanding of potentially different pathogenetic pathways by studying the gene profiles of autoantibody subsets of SSc.

Methods: Blood samples were collected by phlebotomy and preserved in PAXgene tubes (Qiagen). The PAXgene tube's composition stabilizes the cellular RNA profile and can be stored at -80 C for a prolonged period of time. Twelve samples each from autoantibody subsets of SSc: anti-centromere, anti-RNA polymerase III, and anti-topoisomerase-I; lupus cases and healthy controls were grouped by age and gender. Lupus was used as an additional control for SSc samples because it is a known autoimmune disease with autoantibodies and type I interferons playing key roles in its pathogenesis. SSc cases were selected on the basis of more recent active disease. The RNA was extracted using kits from Qiagen and quality confirmed by Nanodrop ND-1000 spectrophotometer. RNA from whole blood has a preponderance of globin genes which may create a bias in the gene expression profile and thus were removed by using the globin reduction protocol from Ambion. The whole genome gene expression profile will be studied using Illumina HumanRef-8 arrays containing > 24000 probes.

Results: We were able to demonstrate the successful extraction of RNA from PAXgene tubes frozen for > 12 months. The RNA yields ranged from an average of 3-16 µg from 2 ml of whole blood. We will use these RNA samples for the performance of gene expression arrays, and these data will be shown at a later time.

ABSTRACT

Effect of COX 1 Regulation by GPx in Presence of Liposomes

CARTER D POAGE *The University of Texas at Austin* **Class of 2008**

Sponsored by: Richard J Kulmacz, Ph. D. Departments of Internal Medicine – Hematology and Oncology

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

Key Words: prostaglandin H synthase, glutathione peroxidase, glutathione, liposome

Prostaglandin H synthase-1, also known as cyclooxygenase-1 or COX-1, resides in the endoplasmic reticulum and nuclear membranes and its substrate (arachidonic acid), product (prostaglandin G2), and activator (lipid peroxides such as prostaglandin G2) are all relatively hydrophobic. Thus, COX-1 reaction kinetics may be influenced by binding of the detergent-solubilized, purified enzyme to phospholipid liposomes. The purpose of this study was to examine the effect of liposomes on the efficiency of COX-1 feedback activation by lipid peroxide. COX-1 activation efficiency in the presence and absence of liposomes was assessed by measuring the activity of a fixed amount of the enzyme in assays with increasing amounts of glutathione peroxidase (GPx), which suppresses COX-1 activity by reducing the prostaglandin G2 required for COX-1 activation. The activity of the GPx stock solution was determined with a standard assay. The COX-1 activity with each level of GPx was determined from a coupled assay using the peroxidase activity also catalyzed by the COX-1 protein. The liposomes were extruded from a suspension in 50 mM Tris, pH 7.5, of either dimyristoyl phosphatidylcholine (C14PC), dioleoyl phosphatidylserine (DOPS) ± oleic acid (OA) (7:3:0.09) or dioleoyl phosphatidylcholine (DOPC), DOPS ± OA (7:3:0.09). COX-1 is known to bind well to DOPC/DOPS/OA liposomes, but poorly to liposomes with the other compositions. Two experiments with C14PC/DOPS/OA liposomes produced conflicting results, one indicating that the liposomes increased the activation efficiency, the other showing no effect. An additional experiment with DOPC/DOPS liposomes indicated no change in COX-1 activation efficiency. Additional experiments are in progress.

ABSTRACT

Linking Renal Failure with TAAA Repair

MARY E. POSTEL *Boston College* Class of 2009

Sponsored by: Charles Miller III, PhD
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Renal Failure, CPK, TAAA repair

Renal failure following thoracoabdominal aortic aneurysm (TAAA) repair has been reported to range from 20 to 40%, with associated mortality up to 60%. Mechanisms have been difficult to identify and treatments difficult to find. We hypothesized that ischemia might have an indirect effect on the kidney via distant metabolic processes; thus, we studied the effects of the ischemic stress biomarker creatine phosphokinase (CPK) on risk of renal failure following TAAA repair.
We reviewed 55 cases with complete data. Main and interaction effects of CPK with aortic crossclamp time on risk of renal failure and mortality were estimated using multiple logistic regression analysis.

Strong interactions between aortic crossclamp time and CPK were detected with respect to risk for renal failure and mortality, with main effect p values for clamp time and CPK $p<0.003$ and <0.05, respectively, and interaction $p<0.04$. When CPK was below 3000, the relationship between crossclamp time and renal outcome and mortality outcome was normal, with probability of outcome increasing with increasing crossclamp time. When CPK was greater than 3000, the inverse was true; shorter crossclamp times were associated with increased renal morbidity and mortality.

The interaction effects for both renal failure and mortality suggest that an abnormally high CPK in the absence of a long clamp time is a grave prognostic sign and probably represents poor ischemia tolerance. A major question for the future is whether myoglobin is elevated when CPK is high, and whether this is out of proportion to clamp time or GFR.

ABSTRACT

Salivary Cytokines as Diagnostic Markers for Breast Carcinoma

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Sponsored by: Charles F. Streckfus DDS, MA, FAOM Professor Diagnostic Sciences UTHSC-Dental Branch

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

Key Words: Bioplex cytokine immunoassay, breast cancer, salivary analysis, cytokines

The link between disease and the oral cavity represent two clinically important factors that have given rise to the interest in using saliva as a diagnostic fluid for systemic diseases. Recent advances in molecular technology in the analysis of saliva are increasingly being used to diagnose disease and predict disease progression such as cancer. This study describes the use of Bioplex cytokine immunoassay to detect the presence of cancer related cytokines in the saliva of women with breast cancer. A multiplex analysis of 12 different cytokines (interleukin (IL)-1β , IL-4, IL-6, IL-8 IL-10, IFN- γ, EGF, TGF- α, TNF- α, RANTES, MCP-1 and VEGF) was performed on pooled cancer saliva specimens (n = 8), specimens from healthy women (n = 10), benign (n = 10), women diagnosed with breast cancer (n = 52), and pre op (n = 21) and post op (n = 10) specimens. These specimens were assayed on the Bioplex suspension array. All of the cytokines were detected in saliva however, the IL-1β, EGF, TGF- α, VEGF and MCP-1, exhibited the most potential diagnostic utility. We also noted that these cytokine concentrations could be modulated as many of them exhibited a decrease in concentration after the tumor was removed (1 year post op). Concentration differences in the cytokine levels were noted between the healthy, benign, and the cancer groups. This study indicates that the presence of cancer related cytokines in saliva may have utility for monitoring patient response to chemotherapy.

ABSTRACT

Regulation of CaMKII Phosphorylation by the Postsynaptic Density

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Sponsored by: M. Neal Waxham, Ph.D., Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: postsynaptic density, cell signaling, protein phosphatase, protein kinase

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is found within the postsynaptic density (PSD), a cytoplasmic structure underneath the postsynaptic membranes of CNS glutamatergic synapses. Following autophosphorylation of Thr^{286}, CaMKII is capable of achieving a partially calcium-independent state in the enzyme's regulatory domain and such activation is believed to serve as a molecular memory mechanism. CaMKII may phosphorylate specific receptors in the PSD membrane after autophosphorylation to produce chemical changes that strengthen the synapse and promote long-term potentiation (LTP). Conversely, the dephosphorylation of CaMKII may be carried out by a variety of PSD phosphatases such as PP1 or PP2A. The relative rate difference between the rapid forward and sluggish reverse reactions has been implicated as a possible mechanism employed by the nervous system to promote LTP. In order to determine the relative involvement of different phosphatases in the dephosphorylation of CaMKII, this study employed a variety of phosphatase inhibitors in ^{32}P-radiolabeling assays with CaMKII-containing PSDs and purified CaMKII with PP1 after the phosphorylation reaction had been chemically blocked. The inhibitors greatly reduced the amount of measured CaMKII dephosphorylation in both PSDs and purified CaMKII, but were unable to completely block the reverse reaction, even when used in tandem. Inhibition of CaMKII dephosphorylation in PSDs was greatly improved when the structure was "opened up" using dithiothreitol, supporting previous hypotheses about the spatial complexity of the PSD. It was also found that dephosphorylation of purified CaMKII still occurred in the absence of PP1 and may therefore be capable of occurring independently of known phosphatases.

ABSTRACT

TGFBR1 Mutation with Predisposition to Aortic Aneurysms/Dissections in the Absence of Initial Aortic Aneurysms

SUZANNE E. SMART *Texas A&M University* Class of 2008

Sponsored by: Dianna M. Milewicz, M.D., Ph.D., Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: TGFBR1, aortic aneurysms/dissections, Marfan syndrome

Patients with *TGFBR1* and *TGFBR2* mutations present with aortic aneurysms/dissections but can develop aneurysms/dissections of other arteries. A *TGFBR1* mutation family initially presented with peripheral arterial disease rather than aortic disease. The proband is a 47-year-old woman with a history of two myocardial infarcts and multiple arterial aneurysms/dissections. She had a myocardial infarct at age 37 and underwent bypass surgery. Her second infarct occurred at age 47 and was treated by balloon angioplasty. During the cardiac catheterization, the left internal mammary artery bypass graft dissected. A healed dissection was observed in the large ramus intermedius. A CT-scan uncovered chronic dissections of the vertebral arteries and left internal carotid artery, and a pseudoaneurysm of the right vertebral artery. At the same time, her aortic root measured 4.2 cm by echocardiogram. The proband's mother died of a cerebral aneurysm rupture at age 39. The proband was initially evaluated for Ehlers-Danlos syndrome, vascular type (EDS4), because of her thin lips and skin findings including easy bruising, varicose veins, and thin, translucent, aged skin on her hands and feet. When the biochemical analysis was negative for EDS4, *TGRBR1* and *2* were sequenced and a mutation (G312S) in exon 5 of *TGFBR1* was found. The proband's father did not have the mutation, and presumably the proband inherited it from her mother. The proband's 16-year-old son had an enlarged aorta, exhibited a Marfanoid habitus, weighed 209 lbs., and measured 6'9''. Of four children, he was the only one with the mutation. Although *TGFBR1* mutations have been associated with increased risks for aortic aneurysms/dissections, the proband and her mother did not present with aortic disease. This family is the first to illustrate that *TGFBR1* mutations can present initially with peripheral arterial disease rather than aortic disease.

ABSTRACT

Composition of GP IX in the Platelet GP Ib-IX Complex

MAJA STANOJEVIC *Missouri State University* Class of 2007

Sponsored by: Renhao Li, PhD, Department of Biochemistry and Molecular Genetics
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Glycoprotein, GP IX, antibody

Glycoprotein (GP) Ib-IX-V complex is a platelet adhesion receptor that plays important role in hemostasis. It binds to von Willebrand factor (vWF) under high shear conditions initiating platelet aggregation at sites of injury. It is known that one GP IX is noncovalently bonded to one GP Ibß in the GP Ib-IX complex. Recent studies have shown that two GP Ibß subunits are present in GP Ib-IX complex. The purpose of this study was to assign the number of GP IX subunits present in GP Ib-IX complex. The HA-tag and myc-tag were attached to C-terminal of GP IX using QuickChange mutagenesis kit. Mutated GP IX cDNA was transfected into CHO cells by lipofection. Cell lysates were co-immunoprecipitated with anti-Ibα and anti-IX antibodies. Western Blotting was performed to check if HA tagged GP IX was expressed in the same complex as myc tagged GP IX. Denatured proteins were immunoblotted with HRP-conjugated anti-HA antibody that allowed us to visualize GP IX. GP IX band was detected in cell lysate of αßIX$_{HA}$ when blotted with anti-HA-HRP. In CHO cells transfected with both tagged GP IX subunits, GP IX$_{HA}$ didn't co-precipitate with anti-myc antibody, indicating that only one GP IX subunit was present in the GP Ib-IX complex. The study suggested that one GP IX complex is noncovalently bonded to two GP Ibß subunits in the GP Ib-IX complex.

ABSTRACT

Inducers of *Myxococcus Xanthus 4445* Gene Expression and Starvation-Independent Sporulation

KRISTINA SZENTIRMAY *Georgetown University* Class of 2008

Sponsored by: Heidi Kaplan, PhD, Department of Microbiology and Molecular Genetics
Supported by: Molecular Basis of Infectious Disease Training Grant (T32 A 1055449)
The University of Texas at Houston Medical School - Summer Research Program
Key Words: Gene expression, starvaito-independent sporulation, envelope stress, glycerol, D-amino acids

Myxococcus xanthus is a Gram-negative soil bacterium that undergoes multicellular development and sporulation upon starvation at high density. The *4445* gene is expressed after 2 hr of starvation at high density under control of the EcfA/ReaA/ReaB signaling pathway. This pathway is expected to sense and respond to envelope stresses. The addition of cell-envelope damaging agents such as lysozyme, glycerol (0.5 M), D-amino acids (10 mM) and ß-lactam antibiotics to *M. xanthus* growing cells induces starvation-independent sporulation and ß-lactamase activity. The addition of lysozyme to growing M. *xanthus* cells increases *4445* expression more than 2 fold, suggesting that *4445* expression and ß-lactamase may be commonly induced by cell-wall degradation products. To investigate whether *4445* expression is activated by other cell wall damaging signals such as those produced by glycerol and D-amino acids, 0.5 M glycerol, 10 mM D-methionine and 10 mM D-leucine were each added to cultures of *M. xanthus* cells containing the *4445-lacZ* fusion. The growing cells were monitored for spore formation and ß-galactosidase specific activity every two hrs for eight hrs. Although all of the cells formed spores, only the cells to which 0.5 M glycerol was added induced *4445-lacZ* expression. The mechanism by which 0.5 M glycerol damages the cell wall is unknown, but addition of high concentrations of D-amino acids to growing *Escherichia coli* cells has been documented to inhibit both peptidoglycan synthesis and cross-linking. These data suggest that glycerol and D-amino acids do not generate a common inducer of the starvation-independent development pathway.

ABSTRACT

Simple Screening Method for Determining the Presence of EVER2 Mutation in Families with a History of Epidermodysplasia Verruciformis

MEGHAN THOMEER *University of Texas at Austin* *Class of 2007*

Sponsored by: Stephen K. Tyring, MD, PhD, Department of Dermatology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Epidermodysplasia Verruciformis, EVER 2, HPV

Epidermodysplasia Verruciformis (EV), a rare genetic disease, causes individuals to be susceptible to EV related Human Papillomaviruses (HPV). EV is often characterized by lesions resembling pityriasis versicolor or plane warts. Mutations on the EVER2 gene are linked to EV and may provide insight into the genetics of EV. Some EV HPVs have been linked to skin cancer making detection and understanding of this disease a cornerstone in prevention. Using a simple screening method, it is possible to determine whether a gene mutation found in an individual runs in the family. The mutation was found using SSCP (Single Stranded Conformation Polymorphism) Screening. In order to begin the search for the EVER2 mutation, the suspected gene sequence was checked using BLAST. A TAG stop codon was found within the sample's sequence. This nonsense mutation was absent from the normal gene, therefore, the enzyme MaeI, which cuts at C↓TAG, was used. The gene sequence for EVER2 was amplified using Hot Start PCR. The PCR product was purified using Centrifugal Filter Device. The presence of the product was determined by running it on a 2% Seakem LE gel. Once the gene sequence was digested with the enzyme, the results were run on a 3% Seakem LE gel. The digestion showed the Mutation to be present in all members of the family with known EV. Moreover, the mutation was homozygous as evidenced by the presence of only 2 lines that together were the length of the uncut control and undigested DNA. This simple screening method can be used to identify family members at high risk and assist in genetic counseling.

ABSTRACT

Differential Expression of p63 and p16 to Distinguish Squamous Cell Carcinoma *in situ* from Actinic Keratosis

DANIEL WANG *University of Texas at Austin* *Class of 2007*

Sponsored by: Stephen Tucker, MD, Department of Dermatology
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Squamous cell carcinoma *in situ*, actinic keratosis, p63

Currently squamous cell carcinoma in situ (SCC in situ) and actinic keratosis (AK) lack a clear means to be properly delineated, which causes difficulty in properly assigning diagnosis. P63 is an anti-apoptotic gene in the same family as the pro-apoptotic genes p53 and p73, while p16 is a tumor suppressor gene with an inverse expression to retinoblastoma protein, another tumor suppressor and cell cycle regulator. Thus p63 and p16 were chosen for immohistochemical staining of squamous cell carcinomas and AKs to see if the two cancers expressed p63 and p16 in characteristic patterns during early tumorogenesis. Immunohistochemical stains of ten biopsies of Bowen's disease with known arsenic exposure were prepared. Results were intraslide comparisons. Four of the ten p16 stained biopsies had areas of tumor and epiderrnal dysplasia specifically stained brown, and less staining was observed in areas without full epidermal dysplasia, which indicates p16 as a potential marker to differentiate SCC in situ and AK. Nuclear staining of p63 throughout the epidermis was noted in most of the biopsies with dysplastic cells. Heavier staining and a greater portion of stained epidermis were noted in areas of greater epidermal dysplasia. This experiment supports p16 staining as a means to differentiate SCC in situ and AK, while p63 is not as useful. Other genes may be explored, such as GLUT1, survivin, and p120, to determine if their differential expression can better delineate
SCC in situ and AK.

ABSTRACT

Integration of winPFT and winBoxer into the IMIRS 3D reconstruction software package

DIANE L. WANG *University of Texas at Austin* *Class of 2009*

Sponsored by: Hong Zhou, PhD, Department of Pathology, Yuyao Liang, PhD
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Molecular Basis of Infectious Disease Training Grant (T32 AI055449)
Key Words: Image Management and Icosohedral Reconstruction System, three dimensional reconstruction, integration, cryo-electron microscopy

Today, cryo-electron microscopy (cryoEM) and three-dimensional (3D) reconstruction of macromolecular complexes at resolutions below nanometer level is a rapidly advancing field of research, offering valuable insight into the functionality of biological molecular machines. A high-resolution software package, called Image Management and Icosohedral Reconstruction System (IMIRS), complete with a graphical user interface (GUI) and a relational image database, has been developed specifically to reconstruct those molecular complexes displaying icosohedral symmetry, such as the protein capsids of many spherical viruses. However, this software package is still inconvenient to use, namely because the auxiliary programs winPFT and winBoxer need to be accessed separately from the package. The purpose of winPFT is to find the initial orientation and center parameters of particles by using the projection matching method, and that of winBoxer is to box out these particles and calculate the Fourier transform of cryoEM images. As both these programs are crucial to the reconstruction process, having them incorporated into the IMIRS software package will greatly facilitate users. Here, I integrate both of these programs into the IMIRS GUI using the Borland C++ Builder integrated development environment (IDE). As with everything else in the IMIRS package, these programs are fully ported to the Microsoft Windows operating system using Borland C++ Builder 6.0 and Microsoft Visual Studio 6.0. The integration of these otherwise disparate programs into a unified IMIRS package has made cryoEM reconstruction easier and more efficient.

ABSTRACT

Motor Output Can Induce Changes in Perceptions of Audiovisual Simultaneity

WILBUR WANG *Rice University* *Class of 2009*

Sponsored by: David M. Eagleman, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: Audiovisual simultaneity, recalibration, causality, time perception

The brain is highly plastic in its ability to temporally align an organism's perceptions with its actions. It has been found that adaptation to an artificial delay between action and sensation leads to a shift of a human subject's perceived point of simultaneity. To test whether a motor output can change perceived points of simultaneity in the auditory and visual domains, subjects pressed a key that produced a flash and a bang (both with durations of 20 ms) at a distance of 150 feet away. The sound came on at the same time as the subject's key press, and the flash was presented at random times between 0 and 250 ms. Because sound travels 150 feet in 125 ms, the sound was perceived to come on at a constant offset after key press. Ten subjects participated in this experiment in two conditions. In the Motor condition, subjects manually adjusted the delay of the flash and triggered the flash-bang device with motor output (a key press). In the No Motor condition, the device could not be triggered by motor output—instead, the experimenter triggered the device. Subjects adjusted the delay of the flash until both flash and sound were perceived to be simultaneous. There was a significant difference between No Motor and Motor groups in the final adjusted audiovisual offsets ($p < 0.01$). The mean audiovisual offset for perceived simultaneity in the No Motor condition was 120 ms, whereas the mean offset in the Motor condition was 76 ms, implying that the average subject recalibrated in the motor condition by ~45 ms. Further experiments will be needed to understand if a motor act is all that is necessary to induce the effect or if the perception of causality is required to recalibrate the brain to a constant stimulus.

ABSTRACT

Video-based Eye-tracking for Subject Monitoring in fMRI

ESZTER ZAVODSZKY *University of Michigan* *Class of 2009*

Sponsored by: Michael S. Beauchamp, PhD, Department of Neurobiology and Anatomy
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: fMRI, eye-tracking, somatosensory system

Functional magnetic resonance imaging (fMRI) is a technique for non-invasively observing brain function. Behavioral responses are used in many fMRI studies because they allow monitoring of the subject's alertness and provide additional data that can be correlated with brain activation data. Button pressing is the most frequent response method. However, this creates a confound in studies of the somatosensory system: it is difficult to separate the brain activation evoked by the button response from the activations evoked by somatosensory stimulation. Eye-tracking is a potential solution to this problem. We set up an Applied Science Laboratories Series 6000 MR-compatible eye-tracking system, which employs infrared eye illumination via a mirror located in the scanner bore to obtain a bright back-lit pupil and a corneal reflection, which are combined to calculate the subject's point of gaze.

We conducted an fMRI experiment in which we delivered vibrotactile stimuli to subjects' left and right hands. One hand was stimulated in each trial, and the subject indicated the hand on which they felt the stimulus by looking at the appropriate hand on a body diagram. The eye movements in each trial were recorded in real time, and correlated with the stimulus presentation in order to determine reaction time and accuracy. For one subject, we recorded an accuracy of 95.67% and a reaction time of 488±141 (SD) ms. Eye-tracking promises to be an important resource for fMRI studies of somatosensory cortex, as well as for patients whose physical limitations prevent them from responding with button presses.

ABSTRACT

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

JENNY Y. ZHOU *Emory University* Class of 2009

Sponsored by: Heinrich Taegtmeyer, MD, DPhil, Department of Internal Medicine
Supported by: The University of Texas at Houston Medical School - Summer Research Program
Key Words: AMP Kinase, Cardiac Growth, Protein Degradation

Background: Left ventricular hypertrophy increases death and disability from heart failure. Conventional strategies used to reverse cardiac hypertrophy currently 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 and 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: NRVM were treated with two pharmacological activators of AMPK, Metformin (1,1-dimethyl biguanide HCl) and AICAR (5'-phosphoribosyl-5-aminoimidazole-4-carboxamide). Myocytes were lysed and harvested. RNA was isolated and subjected to quantitative RT-PCR. Gene expression was normalized to total RNA concentration. Results: The antidiabetes agent Metformin and AICAR both increased transcript levels of Mafbx/Atrogin 1 and MuRF-1 *in vitro* ($n=8$, $p<0.05$). We also found activation of AMPK and AMPK regulated genes by hypoxia, when cardiomyocytes are energy starved. Future Experiments: The lab will now induce pharmacological activation of AMPK in the H9C2 cell line and transfect them with a dominant negative AMPK adenovirus. In all experiments transcript and protein levels of the ligases will be measured and cell size will be determined in order to provide proof of principle.

Faculty Mentors

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Actor, Jeffrey	57	Pathology
Actor, Jeffrey	77	Pathology
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Actor, Jeffrey	37	Pathology
Albarracin, Constance	27	Pathology – GSBS
Arnett, Frank	72	Internal Medicine
Arnett, Frank	88	Internal Medicine
Beauchamp, Michael	75	Neurobiology
Beauchamp, Michael	80	Neurobiology
Beauchamp, Michael	100	Neurobiology
Bradley, Richard	73	Emergency Medicine
Bull, Joan	82	Internal Medicine
Christie, Peter	34	Microbiology
Clanton, Thomas	15	Orthopaedics
Colasurdo, Guisseppe	32	Pediatrics
Cox, Charles	20	Surgery
Cox, Charles	30	Surgery
Cox, Charles	41	Surgery
Dessauer, Carmen	53	Integrative Biology
Doursoiut, Marie	44	Anesthesiology
Doursout, Marie	17	Anesthesiology
Dragoi, Valentin	83	Neurobiology
DuPont, Herbert	79	Internal Medicine
Eagleman, David	55	Neurobiology
Eagleman, David	99	Neurobiology
Fletcher, Stephen	28	Neurosurgery
Frost, Jeffrey	46	Integrative Biology
Goldschmidt, Millicent	84	Microbiology
Hagberg, Carin	38	Anesthesiology
Hasa, Khader	85	Radiology
Hasan, Khader	70	Radiology
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Johnson, Philip	59	Internal Medicine
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Kaplan, Heidi	86	Microbiology
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Koehler, Theresa	87	Microbiology
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Kozar, Rosemary	54	Surgery
Kulmacz, Richard	89	Internal Medicine
Li, Renho	94	Biochemistry
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Steinberg, Joel	47	Psychiatry
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