<table>
<thead>
<tr>
<th>1. Title</th>
<th>Exploring the physiologic role of 5-HT2A/2C – PSD-95 PDZ domain-mediated interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Atheir Abbas</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Bryan L. Roth</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>CWRU</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Postsynaptic Density 95 (PSD-95), a neuronal MAGUK, is composed of 3 N-terminal PDZ domains and C-terminal SH3 and GK domains, all of which are involved in mediating protein-protein interactions. Immunofluorescent visualization of PSD-95 knockout brain with appropriate receptor-specific antibodies reveals an apparent reduction in 5-HT2A receptor expression along with an almost complete absence of 5-HT2C receptors in regions that would normally express PSD-95. Initial autoradiographic analysis using [125I]DOI, a selective 5-HT2A/2C agonist; as well as saturation binding experiments (using homogenates of micro-dissected brain regions of interest like cortex, striatum, and hippocampus) with [3H]ketanserin directed at the 5-HT2A receptor, have confirmed these findings. Initial experiments using saturation binding experiments ([3H]mesulergine) confirm the large reduction in 5-HT2C receptor expression in PSD-95 knockouts. The net effect of PSD-95 is to increase 5-HT2A/2C receptor expression (and possibly modulate function), but whether or not this is an effect specifically of the 5-HT2A/2C-PSD-95 interaction, or an indirect effect due to the disruption of some other interaction, is difficult to established. In order to better address this problem, I have generated PDZ domain mutants exhibiting high affinity for PDZ ligand motifs. These mutants will be further characterized in vitro, and their potential usefulness in vitro and in vivo will be explored. Finally, we will continue further characterization of the effect of PSD-95 knockout on 5-HT2A/2C receptor function will follow, beginning with an assessment of PSD-95’s impact on Gq-coupled signaling by GTP[−35S] binding in fresh frozen brain tissue. This will determine if the functional</td>
</tr>
</tbody>
</table>
effects parallel the effects on receptor expression. The data thus far provide some of the first in vivo evidence that PSD-95 can indeed modulate the function of its partners, in this case, by affecting 5-HT2A and 5-HT2C receptor expression levels.
**ACKER, SHANNON**

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Analysis of Changes in Gene Expression Induced by Fusion of Dendritic Cells and Melanoma Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Nawal W. Alkharouf</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Gregory Plautz, M.D.</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Gregory Plautz, M.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Center for Surgery Research, Surgery Division</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Cleveland Clinic Foundation; Case School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship; NIH-NCI RO1 CA91981</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>T cell-mediated cancer immunotherapy depends on adequate sensitization to tumor antigens. We have used electrofusion of dendritic cells (DC) with tumor cells (TC) to generate heterokaryons (DC-TC), which continuously express tumor antigens yet possess the antigen processing and co-stimulatory functions of DC. In preclinical models, DC-TC fusion cell vaccines mediate cure of established tumors but the effects of fusion on gene expression are unknown. In this study, we tested the hypothesis that fusion of distinct cell types would lead to alterations in the gene expression pattern for each cell and induce novel gene expression. We used Affymetrix human oligonucleotide arrays to examine the gene expression profile in triplicate samples of DC-melanoma fusion cells (DC-TC) enriched to &gt;95% purity and compared them to DC-DC fusions and TC-TC fusions. Bioinformatics analysis methods, including a relational database, were developed to identify and functionally classify genes with a robust change in expression. Hierarchical cluster analysis of all fusion samples using the entire set of transcripts (n=22,277) separated the fusions into 3 distinct clusters, with the DC-TC cluster being closer to TC-TC than DC-DC. The DC-TC fusion samples also exhibited a higher Spearman rank correlation coefficient in pair-wise comparisons with the TC-TC samples. In addition, fewer genes were differentially expressed between the DC-TC and TC-TC samples (n=368) compared with DC-DC (n=1,927), and genes that were either upregulated or downregulated in the DC-TC vs. TC-TC or DC-DC fell into distinct functional classes. We also identified a set of 28 unique genes expressed only in DC-TC fusion cells involved in transcription, growth, signal transduction, cell adhesion, extracellular matrix and cytoskeletal organization. Interestingly, we observed novel expression of myoferlin, a protein involved in the physiologic process of Ca+2-mediated...</td>
</tr>
</tbody>
</table>
membrane fusion of myoblasts. These findings provide novel information about changes in and regulation of gene expression in the unique case of heterokaryon formation.
Toll Like Receptors in Fusarium Keratitis

Bishr Aldabagh

Ahmad Tarabishy, M.D

Eric Pearlman, Ph.D

Ophthalmology, Pathology

Case Western Reserve University, University Hospitals

MSTP Program

MD PHD

2

Purpose: Fusarium keratitis is an ulcerative corneal disease which is destructive to the ocular structures and detrimental to vision. Fusarium will penetrate the cornea and Descemet’s membrane if untreated and contiguously spread into the anterior chamber and eventually lead to endophthalmitis. This study examines Toll Like Receptor (TLR) responses to clinical isolates of Fusarium keratitis using TLR2, TLR4, TLR2/4, and MyD88 null mice.

Methods: The corneal epithelium was abraded and exposed to heat killed Fusarium (conidia and hyphae) at a concentration of 5 x 10^6 CU/mL diluted with hydroxypropyl methylcellulose ophthalmic demulcent and covered with plastic or filter membrane to secure the fungal solution. Confoscan analysis and immunohistochemistry were performed at 24 hour time points. In vivo analysis was performed using Green Fluorescent Protein positive bone marrow chimeric mice to track the kinetics of the host response in vivo. Neutrophils and macrophages were isolated from wild type and TLR mice using a continuous gradient after intra-peritoneal injection of casine and stimulated with Fusarium to determine a dose response to fungal load.

Results/Conclusion: In vitro studies show a decreased chemokine response to Fusarium (both hyphae and conidia) in both the TLR2 null and TLR4 null mice. Heat killed Fusarium did not induce a response in vivo but showed a decreased response compared to the control. Thus, Fusarium may be inhibiting the immune response.
| 11. What was your role in this project? | Plan and execute experiments |
### 1. Title
The effects of altering pacemaker rates on cardio-ventilatory coupling

### 2. Student Presenter:
Andrew Aladi

### 3. Co-workers and Collaborators:
Christopher Miller

### 4. Advisor:
Kingman Strohl

### 5. Departments:
Division of Pulmonology, Department of Medicine

### 6. Institutions:
VA Medical Center

### 7. Support:
T35 Award

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)
Ventilatory behavior (breath timing and tidal volume) and cardiac rhythm are produced by brainstem neural systems. Ventilation and cardiovascular rhythms are non-randomly coupled. This study investigates the hypothesis that in patients with pacemakers, changing the pacing within the normal physiological range has an effect on cardio-ventilatory coupling. Pacemaker patients (4-6) recruited by doctor referral and who meet exclusion criteria are completing a questionnaire regarding their general health, including age, weight, height, chronic medical problems, reason for pacemaker treatment, diagnosis of heart and lung disease, prescription medications, OTC medications, smoking history, allergies, surgery in the last 6 months, sleep disorder, time of last meal, or any caffeinated drinks today. The procedure is explained to the patients and informed consent is obtained. Measurements of ventilation are made through a mouthpiece wearing noseclip, using a pneumotachograph on the inspiratory side of a one-way valve. Heart activation (HA) and R-R interval are measured by electrocardiogram from a modified V5 lead placement. The subjects are seated comfortably with their heads reclined at an angle of 30 degrees in a quite room at approximately 70 F. Subjects were allowed to become accustomed to the mouthpiece and nose clip before data recording was started. The pacemaker is then varied in the normal physiological range between high, medium and low rates for approximately 10 minutes. Entropy values are calculated for the following intervals: HA to start of inspiration, HA to start of expiration, the start of inspiration to HA, and the start of expiration to HA. For each interval, the entropy value for each subject is determined. These values will be compared at high, medium and low pacing rates. The entropy values will be compared between pacing rates to determine if the cardio-ventilatory rate is uncoupled and which precedes the other. Data analysis is pending.
| 11. What was your role in this project? | Performed study |
### 1. Title
Are breastfeeding intentions of pregnant teens different?

### 2. Student Presenter:
Ashley Alexander, B.A.

### 3. Co-workers and Collaborators:
Mary Ann O’Riordan, M.S.

### 4. Advisor:
Lydia Furman, M.D.

### 5. Departments:
Pediatrics

### 6. Institutions:
Rainbow Babies and Children’s Hospital

### 7. Support:
Crile Grant

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)

**Background and Rationale:** Risk factors for low breastfeeding rates include lower educational level and socioeconomic status, non-Hispanic African-American (AA) ethnicity and younger age. Little research, however, has focused on barriers to breastfeeding specifically among high risk teenage mothers. Since teens may have different barriers to breastfeeding than older women, an understanding of teen mothers’ attitudes and knowledge towards breastfeeding is critical to design and implementation of interventions.

**Hypothesis:** Pregnant teenagers (15-19 years old) will have a lower rate of intent to breastfeed, different attitudes, and less knowledge about breastfeeding than pregnant adult women (>20 years old).

**Methods:** With IRB approval, we conducted structured interviews of consecutive eligible pregnant women receiving obstetrical care at the Women’s Health Center, MacDonald Women’s Hospital, Cleveland, OH (6/1-7/31/07). The questionnaire included sociodemographic factors, and 34 questions focused on six conceptual domains: breastfeeding experience, planning/abstract thinking, concerns about breastfeeding, the influence of family and friends, knowledge of and ability to use resources, and body image. The primary outcome measure was the rate of intent to breastfeed among teen vs. adult participants.

**Results:** We interviewed 176 pregnant women (95% AA, 94% single marital status) of whom 46 were teens and 130 were adults. There was no difference between teens and adults in either rate of intent to
breastfeed (63.0% vs. 60.0% respectively, p=0.83), in planned duration of breastfeeding (p=0.79), or in plan to breastfeed exclusively (24.1% vs. 42.3%, respectively, p=0.23). Additionally, almost all measured attitudes and knowledge about breastfeeding were not significantly different between the pregnant teens and pregnant adult women.

Conclusions: Within a population with sociodemographic risk for low rates of breastfeeding, we found no difference in prenatal breastfeeding intentions between adults and teens. The implication of this finding is that one targeted breastfeeding intervention program should be effective for both adults and teens in this high risk population.

11. What was your role in this project?

Consented and interviewed subjects, did data entry
<table>
<thead>
<tr>
<th>1. Title</th>
<th>PARACEST agents for DCE MRI studies of tumor angiogenesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Raphael Alford</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Byunghee Yoo, Meser Ali</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Mark Pagel</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Biomedical Engineering</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University, University Hospitals</td>
</tr>
<tr>
<td>7. Support:</td>
<td>This project was funded by the American Cancer Society through the Case Comprehensive Cancer Center in September 2004-December 2005.</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Changes in tumor angiogenesis are an early biomarker of aggressive cancer growth and chemotherapeutic efficacies. It has been shown that vascular permeability is correlated with angiogenesis. However, standard MRI methods that measure tumor angiogenesis are qualitative or semi-quantitative, due to biological variabilities. PARACEST agents are paramagnetic lanthanide complexes that can be selectively detected with MRI, so that the multiple agents can be measured during one MRI scan. We hypothesize that PARACEST agents with different diameters can be simultaneously applied to a tumor animal model and sequentially detected, so that DCE MRI vascular permeability characteristics can be measured from all imaging probes during a single MRI scan session. The assessment of multiple agents during the same scan session will reduce or eliminate problems with biological variabilities. PARACEST agents were characterized in vitro to optimize image enhancement parameters. Preliminary tests with a PARACEST agent that targets liver tissue were also conducted to optimize in vivo imaging. MCF-7, MCF-7C3, and MB-468 tumor models were developed for ongoing studies of PARACEST agents for DCE MRI applications.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Researcher</td>
</tr>
<tr>
<td>1. Title</td>
<td>Sleepiness and Executive Function: Subjective and Objective Measures</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Basil Anderson</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Storfer-Isser, Amy, Taylor, H. Gerry, Spilsbury, James, Emancipator, Judy, and Redline, Susan</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Susan Redline</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>T35 Scholarship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Sleep loss can have severe detrimental consequences for adolescents and children. Few studies of sleep have looked at subjective and objective measures of sleep. The hypothesis of this study was that objective and subjective measures of sleepiness would be significantly associated with both objective and subjective measures of specific measures of executive functioning in a community-based sample of adolescents. Adolescents were selected from the Cleveland TeenZzz study. Sleep time measured by Actigraphy and Sleepiness measured by the modified Epworth Sleepiness Scale (ESS) were used as measures of sleepiness and sleep loss. The DKEFS and BRIEF were used as measures of executive functioning. Sleepiness (based on ESS scores) was highly correlated with BRIEF scores even after controlling for multiple confounders. Sleepiness was correlated with scores on the DKEFS, but this correlation was attenuated when confounders were controlled for. Reduced sleep time measured by actigraphy was not significantly associated with any outcomes. Subjective but not Objective measures of sleepiness were correlated with impaired executive functioning. Further research needs to examine objective measures of sleepiness and the best way to quantify sleepiness.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Background research, Paper writing, Data analysis and interpretation</td>
</tr>
</tbody>
</table>
**1. Title**
Modulation of antigen-specific CD4+ T cell responses during pulmonary mycobacterial infection

---

**2. Student Presenter:**
Mursalin Anis

---

**3. Co-workers and Collaborators:**
Scott Fulton, Scott Reba, Clifford V. Harding, W. Henry Boom

---

**4. Advisor:**
W. Henry Boom

---

**5. Departments:**
Pathology and Infectious Diseases

---

**6. Institutions:**
Case Western Reserve University School of Medicine

---

**7. Support:**
HL07889

---

**8. Please choose your academic program:**
MD PHD

---

**9. What year are you in the program?**
6

---

**10. Body of Abstract (300 words or less)**

We hypothesized that ongoing pulmonary mycobacterial infection would modulate recruitment and activation of naïve antigen-specific CD4+ T cells. Balb/c mice were infected with aerosolized Mycobacterium bovis-BCG. Four to six weeks later, CFSE-labeled DO11.10 T cells, specific for OVA323-339:I-Ad, were adoptively transferred into naïve or infected mice. Recipient mice were challenged intra-nasally with soluble ovalbumin (OVA) over 3 days and then lungs, mediastinal lymph nodes (MLN) and spleens harvested to measure DO11.10 T cells by flow cytometry. To monitor antigen-specific T cell proliferation in vivo CFSE dye dilution and BrdU incorporation by DO11.10 cells was measured. Based on CFSE dilution profiles, responder frequencies of OVA-specific T cells in the BCG+OVA mice in MLN, lungs and spleens were 53(±2)%, 31(±3)%, 8.6(±1)% respectively. Responder frequencies in OVA mice were 46(±7)%, 13(±1)%, and 4.7(±1)%. ELISPOT showed increased frequencies of IFN-g secreting cells in the lungs of BCG+OVA vs. OVA alone mice. Pulmonary infection with BCG alone did not recruit appreciable numbers of OVA-specific T cells: recruitment required the presence of OVA. Ongoing pulmonary BCG infection increases recruitment, activation, and IFN-g secretion of pulmonary CD4+ T cells that encounter airway antigen.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Nutrition in Polytrauma Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Shohrat Annaberdyev</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Heather Vallier, M.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Dept. of Orthopaedics at MetroHealth Hospital</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td></td>
</tr>
<tr>
<td>7. Support:</td>
<td>T35</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Background and Rationale: Trauma causes increased stress on patients, which consequently leads to increased GI acid production as well as increased translocation of bacteria across the gut. This poses a greater risk of bleeding and infection. The problem of providing adequate nutrition to support the healing process is further complicated by the hypercatabolic response elicited by major trauma. Patients frequently require operations and are frequently made NPO perioperatively. Diminished nutritional status of hospitalized trauma patients results in slower fracture and wound healing, and increased risks of infection. In states of acute malnutrition, protein catabolism for prolonged periods is associated with increased strain on cardiac, pulmonary, hepatic, GI and other organ systems, making patients more susceptible to infections, which is detrimental to wound and fracture healing.

Hypothesis: Early enteral feeding will reduce complications, length of stay, and costs, when compared with delayed enteral nutrition, or parenteral nutrition (e.g. i.v. proteins, lipids, sugars).

Methods: The study is a retrospective review of 419 patients with multiple system injury, including orthopaedic trauma, defined as unstable spine, pelvis, acetabulum, or femur fracture requiring surgery, or a surgical repair involving greater than or equal to two extremities. Data is collected through chart review, and patients are contacted to conduct an outcomes questionnaire – MFA (Musculoskeletal Function Assessment).

Results: The data collection is still not complete. While extensive chart review and data was collected on 114 patients, it is still early for concrete analysis or preliminary results.
Conclusions: Upon conclusion of the study, the specified patient population will be evaluated for complications, number of days spent on ventilator, number of days in ICU, and MFA outcomes. These will be analyzed for associations with type of feeding (PO vs NPO) that was administered to the patient, as well as early vs delayed initiation of PO feeding.

| 11. What was your role in this project? | Data collection, patient contact. |
**ARNAUD, MAYA**

| 1. Title | There Is a High Correlation between the Clomiphene Challenge Test, Antral Follicle Count and Ovarian Volume to Predict the Ovarian Reserve |
| 2. Student Presenter: | Maya E. Arnaud |
| 3. Co-workers and Collaborators: | Arjun Khosla |
| 4. Advisor: | J. Ricardo Loret de Mola |
| 5. Departments: | Department of Reproductive Biology, Department of Obstetrics and Gynecology |
| 6. Institutions: | Case Western Reserve University, MacDonald Women’s Hospital |
| 7. Support: | |
| 8. Please choose your academic program: | MD |
| 9. What year are you in the program? | 2 |
| 10. Body of Abstract (300 words or less) | Objective: Diminished ovarian reserve is a condition occurring in women at any adult age. Among the most common tests employed to diagnose the problem are basal tests for FSH, LH, estradiol and inhibin B, or dynamic endocrine tests such as the clomiphene citrate challenge test (CCCT). The CCCT can unmask patients who might have not been detected by basal FSH screening alone, and appears to be more sensitive than day 3 FSH. In recent years, great attention has been devoted to direct ultrasound tests such as the antral follicle count and ovarian volume. Abnormal values in any of these tests are correlated with a decrease in pregnancy rates. The objective of our study is to evaluate if the CCCT correlates well with ultrasonographic studies such as the ovarian volume and the antral follicle count (AFC) to predict the ovarian reserve. Design: Retrospective cohort study in a University based tertiary Reproductive Endocrinology and Infertility Program Materials & Methods: 391 patients were enrolled in the study. The mean age of the subjects was 35.4 years +/- 4.5. Fifty subjects were smokers. On the month of their clomiphene challenge test (CCCT), antral follicle count (AFC), ovarian volume measurement by ultrasonography and basal gonadotropin concentrations were determined on day 2-3 of a spontaneous period and on day 10 after the CCCT. Serum levels of the various markers of ovarian reserve (FSH, LH, estradiol, progesterone, and antral follicle count) were measured by ELISA in a clinical laboratory. Statistical analysis was performed using simple regression analysis and analysis of variance (ANOVA). Results: There were 48 subjects who failed the CCCT. There was a strong direct correlation between age and day 3 FSH (p<.0001), day 10 FSH (p<.0001); as well as a strong reverse correlation with ovarian volume (p<.007), and the AFC (p<.0001). The mean antral follicle count among patients that passed the CCCT was statistically higher (5.75 +/- .311) than among |
patients that failed the test (2.58 +/- .822) (p<.0004). Additionally, the mean ovarian volume among patients that passed the CCCT was significantly larger (17.36 +/- .816 mm3) than among patients who failed the test (12.944 +/- 1.36 mm3) (p <0.04). Discussion: There is a strong correlation between age and studies that assess the ovarian reserve. There was also a strong correlation between the CCCT, gonadotropin serum measurements and ultrasonographic measurements for the ovarian volume and the AFC. It appears that these studies can be used interchangeably to assess the ovarian reserve.
**Title**
Palliative care in orthopaedic surgical oncology

**Student Presenter:** Pamela M. Aubert

**Co-workers and Collaborators:**

**Advisor:** Dr. Richard J. O’Donnell

**Departments:** Orthopaedic Surgery Oncology

**Institutions:** University of California San Francisco, Comprehensive Cancer Center

**Support:**

**Please choose your academic program:** MD MA

**What year are you in the program?** 2

**Body of Abstract (300 words or less)**
Hundreds of thousands of Americans are affected every year by skeletal complications of oncologic disease. Recent developments in medical oncology, radiation oncology and radiology, particularly with respect to the use of bisphosphonate medication and radiofrequency techniques, have served to greatly lessen the morbidity associated with metastatic skeletal disease. Similarly, there has been significant advancement in the field of orthopaedic oncology in the areas of internal fixation, endoprosthetic implant design, and minimally-invasive kyphoplasty technology. Given the palliative intent of intervention in this patient population, the goal of treatment of skeletal metastases must be optimization of limb function and ultimately, quality of life.

**What was your role in this project?** researcher and first author
**1. Title**
In vivo Imaging of Schistosomiasis Using MicroPET Scanning

**2. Student Presenter:**
Jason D. Balkman

**3. Co-workers and Collaborators:**
Erica Waite, Jeff Kolthammer, Deborah Sim

**4. Advisor:**
James P. Basilion, Christopher L. King, Zhenghong Lee

**5. Departments:**
Center for Global Health & Diseases, Center for Imaging Research, Radiology

**6. Institutions:**
Case Western Reserve University

**7. Support:**
"Research Training in Heart, Lung, Blood & Sleep Disorders", grant number HL082544

**8. Please choose your academic program:**
MD

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**
Diagnosis of schistosomiasis involves the detection of schistosome eggs in the feces and urine of infected individuals. However, this method is unreliable for measuring disease burden because of wide variances in egg shedding. In vivo imaging of schistosome parasites could facilitate better diagnosis, treatment, and management of the disease through more accurate estimations of infection. Moreover, such imaging would provide a valuable tool to study potential atypical locations of the parasite as well as its basic biology. Adult schistosomes are prodigious consumers of glucose, up to 26% of their dry weight in 1 hour. The following work exploits this high metabolic rate using Positron Emission Tomography (PET) to image schistosomes in vivo. We hypothesize that fluorodeoxyglucose (FDG), a glucose analog and PET tracer will be taken up by schistosomes to allow imaging of the parasite. In vitro incubations of parasites with FDG were performed at the skin and adult hepatic portal (3-4 weeks post-infection) stages of development. MicroPET imaging of 4 week post-infected mice anesthetized with isoflurane was conducted 90 minutes after FDG injection via tail vein. Schistosomulae were shown to be FDG avid in vitro, with a 50-100 times greater uptake per worm in the hepatic stage of development when compared to the skin stage. PET imaging of 4 and 6 week post-infected mice show evidence of preferential FDG uptake in the mesenteric region. Additionally, images of 4 week post-infected mice treated with Praziquantel show diminished tracer signal in longitudinal studies. These results demonstrate the potential utility of PET for the imaging of schistosomiasis in vivo. Thus, it is likely that PET technology could serve as a practical tool for the diagnosis, treatment, and management of this disease.
| 11. What was your role in this project? | Project Leader |
### 1. Title
Developing Fluorescence Imaging Methods for Dynamic Cellular Interactions in the CNS

### 2. Student Presenter:
Emi Bays

### 3. Co-workers and Collaborators:
Emi Bays, Deb Barkauskaus, Charles Su, Joseph Nthale, Rachel Liou, Caryn Tong & Alex Y. Huang

### 4. Advisor:
Alex Huang, M.D., Ph.D.

### 5. Departments:
Division of Pediatric Hematology / Oncology; Department of Pediatrics

### 6. Institutions:
Case Western Reserve University School of Medicine; Cleveland, Ohio 44106 USA

### 7. Support:
Dana Foundation Program in Brain and Immune Imaging
T-35 Short-term Research Training Grant entitled: "Research Training in Heart, Lung, Blood & Sleep Disorders"

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)

**Background:** Inappropriate immune tolerance and autoimmunity are immunopathologies manifested as diseases such as cancer and multiple sclerosis. Comprehension of the processes underlying such pathologies requires the study of dynamic interaction on the level of the individual cell. Such focused observation requires the use of techniques beyond static tissue analysis in vivo or dynamic studies of dissociated cells in vitro.

**Hypothesis:** The study of migratory behavior of immune cells in situ – how they are recruited, distributed and their relationship with the surrounding microenvironment – is critical in understanding the spatial and temporal nature of pathogeneses such as cancer and MS.

**Methods:** In order to capture dynamic images of the CNS in an anesthetized mouse, a 2-photon laser scanning microscope (2P-LSM) was utilized, which allowed direct visualization of immune cell behavior deep in living tissues[1,2]. Stereotactic stages and surgical techniques were developed to obtain such images. Anesthesia was induced by injecting 200-250 ul Avertin (200-250mg/ mouse) intraperitoneally (I.P.) or by administering inhaled isofluorane given through a custom-made mask. After induction the animal’s hair was removed from the scalp with clippers and Nair. A vertical incision was made to expose the underlying skull. The mouse was then observed under the 2P-LSM.

**Results:** At the conclusion of the 8 weeks, the following results were obtained: 1) development of stereotactic stages utilized for acquisition of stable live-animal images; 2) creation of effective methods for anesthesia;
3) visualization and generation of serial dynamic images of stem cell repopulation in the bone marrow; 4) visualization of cellular elements in the CNS.

Significance: Understanding the changes of immune cell behaviors in situ will allow for a better understanding of the initiation, control, and maintenance of various immunopathologies. Future goals include refining surgical techniques, obtaining long term images of cell migration, and developing imaging techniques for other anatomical sites including the spine.

References:

<p>| 11. What was your role in this project? | Project Scientist |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Expression of Cyclin A in Alzheimer's Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Jessica Bazick</td>
</tr>
<tr>
<td>3. Co-workers and</td>
<td>Gemma Casadesus</td>
</tr>
<tr>
<td>Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Mark Smith, Ph.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Pathology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve Institute</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your</td>
<td>MD</td>
</tr>
<tr>
<td>academic program:</td>
<td></td>
</tr>
<tr>
<td>9. What year are you in</td>
<td>2</td>
</tr>
<tr>
<td>the program?</td>
<td></td>
</tr>
<tr>
<td>10. Body of Abstract</td>
<td>Alzheimer's disease (AD) is a chronic disorder with progressive neurodegeneration. It is characterized by typical pathological hallmarks including β-amyloid deposition, neurofibrillary tangles, and disturbances in the expression of various cell cycle proteins. Recent findings have suggested that aberrant mitotic re-entry plays a role in the etiology of AD. This study investigates the importance of cell cycle control in AD pathology by focusing on a particular cell cycle protein, cyclin A. Cyclin A forms a complex with CDK2 implicated in eukaryotic cell cycle control. During S phase, CDK2/cyclin A phosphorylates different substrates allowing DNA replication and the inactivation of G1 transcription factors. Immunocytochemistry assays were used to analyze the nuclear expression of cyclin A in neurons in the hippocampi of normal mice and transgenic APP23 mice and in the hippocampi of age-matched human control subjects and patients suffering from AD. The mouse subjects, normal and transgenic, were composed of two different age groups: 3 month old and 12 months old in order to determine whether there was a change in cyclin A levels depending on the age of the mouse. Immunosignal analyses demonstrated no significant difference in cyclin A expression in control subjects and transgenic APP23 mice of either age group. Levels of cyclin A expression were not significantly different in the human control subjects and patients with AD. Even though our analysis did not demonstrate differences in immunosignaling of cyclin A in controls and case subjects, it does not rule out the importance of cyclin A in AD pathogenesis. Levels of the protein from tissue specimens are in the process of being analyzed will provide more information about the expression of cyclin A levels between cases and controls.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>First Author</td>
</tr>
</tbody>
</table>
1. **Title**: Relation of Ventricular Dilatation to Outcome in Infants with Posthemorrhagic Ventricular Dilatation

2. **Student Presenter**: Christopher Beatty

3. **Co-workers and Collaborators**: Maureen Hack, Nori Minich, Dee Wilson

4. **Advisor**: Shenandoah Robinson

5. **Departments**: Divisions of Pediatric Neurosurgery and Neonatology

6. **Institutions**: Rainbow Babies and Children Hospital

7. **Support**: Crile

8. **Please choose your academic program**: MD

9. **What year are you in the program?**: 2

10. **Body of Abstract (300 words or less)**

    **Objective**: Since the 1990’s survival of preterm infants has improved markedly, but children with post-hemorrhagic ventricular dilatation (PHVD) continue to have poor neurodevelopmental outcomes. These children suffer intraventricular hemorrhage (IVH) and other complications of prematurity. The contribution of post-hemorrhagic hydrocephalus to the risk of cerebral palsy and learning disabilities is unclear. We hypothesized assessment of ventricular enlargement and outcomes could clarify the contribution of PHVD to neurodevelopmental outcomes.

    **Methods**: Records of 54 preterm infants from the Rainbow Neonatal High Risk Program database with PHVD were examined. Infants with PHVD without adequate records, imaging, or 20 months (corrected) follow-up were excluded. Severity of illness, dates of ventricular dilatation and treatment, and outcomes were recorded. Lateral ventricular width was measured on coronal head ultrasounds using the standard method of Levine, and noted to be either above or below the 97%+4mm and 97%+50mm lines according to gestational age. Statistical analyses were performed, with P<0.05 considered significant.

    **Results**: Twenty-five infants requiring a permanent shunt were compared to 29 who recovered without a shunt. Infants not requiring a shunt were diagnosed with dilatation significantly earlier (median 12 days) than those needing a permanent shunt (median 26 days, P<0.001). Using the 97%+4mm line, PPV=49% and NPV=80%. With the 97%+50mm line, PPV=80% and NPV=83%, suggesting infants with dilatation >97%+50mm are likely to
require shunting. Multiple statistical analyses failed to demonstrate that PHVD adds significantly to the deficits these children are prone to develop, compared to other risk factors such as IVH.

Discussion:
The accepted threshold (97%+4mm) for ventricular dilatation is not as strong a predictor for requiring a permanent shunt as 97%+50mm. This study shows for the first time a clinically predictive threshold for requiring a shunt in preterm infants. Statistical analyses demonstrated that ventricular dilatation and duration of dilated ventricles did not affect outcomes, unlike IVH.

| 11. What was your role in this project? | Chart Review, HUS measurements |
### 1. Title
OCT Imaging of the Embryological Quail Heart

### 2. Student Presenter:
Jonathan Belding

### 3. Co-workers and Collaborators:
Michael Jenkins, Pankti Patel, Ajay Basavanhally, Osman Chughtai

### 4. Advisor:
Dr. Michiko Watanabe and Dr. Andrew Rollins

### 5. Departments:
Department of Pediatrics, Genetics, and Anatomy
Department of Biomedical Engineering

### 6. Institutions:
Case Western Reserve University School of Medicine
Rainbow Babies and Children's Hospital
Case Western Reserve University

### 7. Support:
NIH T35 Training Grant
AHA Student Scholarship in Cardiovascular and Cerebrovascular Disease

### 8. Please choose your academic program:
MD MS

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)
Optical Coherence Tomography (OCT) imaging is a relatively new modality that is being adapted to study the normally and abnormally developing beating heart. The goal of this project was to provide a detailed atlas of normal quail heart morphology during early developmental stages when it attains its tubular structure and loops to the right (HH stage 10-18) to provide a baseline from which to compare experimentally manipulated hearts. Fixed embryos were studied because resolution and contrast is better than in living hearts. Quail eggs were chosen because they are easy to procure and widely used. Fertilized coturnix eggs were incubated at 100 degrees F and 40% humidity for various times between 36 and 72 hours. The eggs were cracked and the embryos dissected away from the yolk and extraembryonic tissue. They were fixed in 4% formalin for several hours, and washed in PBS solution. The embryos were imaged first by video microscopy and then according to OCT protocol. These files were processed to create a 3D reconstruction of the heart. To date, stage 16, 17 and 18 hearts have been imaged and processed. These images show trabeculae carnae formation in the developing ventricle, dextral looping of the heart, endocardial cushion formation with low cellular density Wharton's Jelly material and the beginning of septation of the outflow tract by these cushions. 3D reconstructions of these hearts show that the external morphology of the mature quail heart is already apparent in these relatively early stages. We believe that this illustrates OCT’s ability to see morphological defects even at these early stages. In conclusion, OCT is a highly useful modality for viewing the normal development of quail hearts at early stages because it is able to image the heart with high resolution. We have the potential to use this technique to...
rapidly and non-invasively image embryos that have been experimentally manipulated.

| 11. What was your role in this project? | Aided in Design and Carried out bulk of research |
1. Title | S3 Heart Sound in the Emergency Department Diagnosis of Heart Failure
---|---
2. Student Presenter: | Justin Benoit
3. Co-workers and Collaborators: | 
4. Advisor: | Dr. William Peacock
5. Departments: | Department of Emergency Medicine
6. Institutions: | Cleveland Clinic Foundation
7. Support: | NIH T35 HL082544
8. Please choose your academic program: | MD
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | Heart failure affects over 5 million Americans, results in 6.5 million hospital days and 12 to 15 million office visits each year and contributes to 300,000 deaths annually (1). Studies have shown that early diagnosis and treatment for heart failure leads to better outcomes for patients and more cost effective care (2), yet even with modern cardiac biomarkers such as BNP, up to 18.5% of heart failure diagnoses are wrong (3). Auscultation of extra heart sounds such as S3 have long been used for diagnosis and prognosis in heart failure (4,5), but the utility of these findings has been undermined by poor accuracy, significant interobserver variability and a decline in physician physical exam skills (6,7,8). Thus, a need exists for better diagnostic tools. A multi-center prospective study was conducted to evaluate the efficacy of Audicor (Inovise Inc, Portland, OR) to electronically detect an S3 in patients presenting to the Emergency Department with acute dyspnea. The acoustic cardiogram was recorded along with a standard 12-lead ECG within 15 minutes of patient presentation. The ability of Audicor to detect an S3 was compared to BNP, and two cardiologists blinded to the results adjudicated the final diagnosis. 1077 patients were enrolled, 238 (22%) had an S3 detected by the machine, and 523 (49%) had a BNP greater than 100 pg/mL. Acute heart failure was diagnosed retrospectively in 432 (40%). Audicor had a sensitivity of 38% and a specificity of 90%, while BNP had a sensitivity of 98% and a specificity of 71%. Thus, Audicor is a good diagnostic complement to BNP for rule-in of heart failure. Logistic regression of S3 to predict 90-day cardiac admission or all cause mortality yielded an odds ratio of 1.52 (1.07 to 2.17, p = 0.021), indicating that Audicor also has prognostic value.


| 11. What was your role in this project? | Collection of patient data |
## 1. Title
Mapping Religious Health Assets in Central America

## 2. Student Presenter:
David Beversluis

## 3. Co-workers and Collaborators:

## 4. Advisor:
Dr. Henry Mosley

## 5. Departments:
Population and Family Health Sciences

## 6. Institutions:
John Hopkins University School of Public Health; Christian Connections for International Health

## 7. Support:
Crile Grant

## 8. Please choose your academic program:
MD MPH

## 9. What year are you in the program?
2

## 10. Body of Abstract (300 words or less)
This Crile project was carried out in conjunction with the ongoing investigations of the Global Religious Health Assets Mapping (GRHAM) project of Christian Connections for International Health (CCIH), a DC-based networking and information sharing organization. GRHAM is an ambitious initiative to quantify, through surveys and onsite GPS mapping, the faith based contribution to primary health care in developing nations, but has not previously worked in Central America.

This researcher participated in a number of activities which have begun the process of mapping FBO involvement in selected Central American countries, including Honduras, Guatemala, El Salvador, Nicaragua, Costa Rica, and Haiti. Significant time was spent compiling contact lists of faith based organizations (FBOs) working in these countries. This was done through the use of internet queries, email correspondence with CCIH contacts in known FBOs, phone interviews with project managers, and access of non-profit and hospital directories, such as Guidestar.org. This effort was coordinated with other interested organizations already active in Central America, such as Medical Mission Exchange.

Training in the use of geographic information systems (GIS) software was also undertaken, and significant effort was put toward geo-referencing approximately 2500 hospital and project sites. This work was carried out by cross-referencing geonet GPS data with known hospital and town locations to produce GIS maps of selected FBO involvement. The World Health Organization’s Healthmapper software was used; this data will eventually be integrated into GRHAM’s online database.
| 11. What was your role in this project? | Researcher |
Near the end of pregnancy, an increase in myometrial responsiveness to circulating estrogens may account for functional changes in human myometrial tissue that convert the uterus to a contractile phenotype. Until recently, the full-length 66 kDa human estrogen receptor α, hERα66, was thought to play the main role in the pregnant myometrium. Within the past decade, a truncated 46 kDa splice variant of this estrogen receptor, hERα46, was identified but has not been examined in human myometrium. The goal of this research project was to explore the levels of these estrogen receptors in human myometrial tissue and their changes during the course of pregnancy. Myometrial tissue samples were obtained from mothers undergoing cesarean sections, either before or after the onset of labor, occurring prior to (<37 weeks) or at term (37-40 weeks). Proteins were extracted and western blot techniques were used to measure the expression of hERα66 and hERα46. Our results showed that hERα46 expression was prevalent in the myometrial tissues of pregnant women, while hERα66 was absent. There was a significant 3-fold increase in hERα46 levels during labor in preterm samples and a trend towards increasing hERα46 expression during labor in term samples. This finding is of great interest, and may correlate with the increased myometrial responsiveness to circulating estrogen near parturition. The molecular mechanism of the shift in estrogen responsiveness remains a mystery, thus warranting additional exploration. Also, further examination of the molecular mechanisms of the action of estrogen would provide a foundation for the development of new strategies to prolong pregnancy to reach term and new treatment modalities for preterm uterine contractions.

Flouriot, G., Brand, H., Denger, S., Metivier, R., Kos, M., Reid, G. et al. (2000). Identification of a new isoform of the human estrogen receptor-alpha (hER-alpha) that is encoded by distinct transcripts and that...
is able to repress hER-alpha activation function 1. The EMBO journal, 19(17), 4688-700.

<p>| 11. What was your role in this project? | Bench research and abstract writing |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Late Phase TNF-alpha Depression in Natural Orifice Translumenal Endoscopic Surgery (NOTES) Peritoneoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>G Bradley Bookatz</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Steve J Schomisch, BS; Jeffrey M Marks, MD; Conor P Delaney, MD, Ph.D; Judy Jin, MD; Christina Williams, MD; Amitabh Chak, MD; David T Matteson, BS; Jaime Andrews, BA; Jeffrey L Ponsky, MD, MBA</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Michael McGee, MD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Surgery</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>University Hospitals Case Medical Center</td>
</tr>
<tr>
<td>7. Support:</td>
<td>ASGE/SAGES NOSCAR 2006 Research Grant</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Natural Orifice Translumenal Endoscopic Surgery (NOTES) allows access to the peritoneal cavity without the skin incisions required by the more traditional methods of laparoscopy and laparotomy. However, contamination of the sterile peritoneal cavity by enteric contents may result in NOTES being more physiologically and immunologically invasive than initially thought. Measurements of Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF-a) have been used as a method to quantify surgical stress. Abdominal exploration was performed on 37 swine via transgastric NOTES peritoneoscopy, laparoscopy (LX), laparotomy (OPEN), or sham surgery (CONTROL). Plasma levels were obtained for TNF-a, IL-1β, and IL-6 at the start and completion of surgery, and at 1 hour, 2 days, 7 days, and 14 days post-operatively. At completion of surgery, the OPEN animals had higher TNF-a levels than all groups. TNF-a levels were similar for all groups at 1 hour and 2 days. Animals that underwent the NOTES procedure had significantly lower plasma levels of TNF-a than all other groups on post-operative days 7 and 14. Analysis was repeated to control for variability in baseline cytokine variability, and confirmed the significantly lower TNF-a levels for NOTES compared to all groups at 14 days. IL-1β and IL-6 levels were undetectable in 66.8% and 70.5% of samples, respectively, without any significant trends. Diagnostic NOTES peritoneoscopy demonstrated similar levels of systemic pro-inflammatory cytokine TNF-a compared to diagnostic laparoscopy and exploratory laparotomy in the immediate post-operative period, as well as consistently decreased levels in the late post-operative period. No group demonstrated a measurable, consistent trend in IL-1β or IL-6 levels. These results indicate an immunomodulatory effect of the NOTES surgical technique not present in laparoscopy or laparotomy.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Lab Assistant</td>
</tr>
</tbody>
</table>
Since attitudes of physicians have been shown to impact their practices, we sought to describe characteristics and attitudes of the oncologists in a study of advanced cancer patients. The Advanced Cancer and Supportive Care Project is a randomized controlled trial testing a coping and communication support intervention that is tailored to the preferences of middle-aged and older late stage cancer patients from near the diagnosis to end of life as the goals of care are expected to shift. The study was conducted in two ambulatory clinics in the Cleveland metropolitan area, (MetroHealth Medical center and the Veteran Affairs Hospital in Wade Park). A 102-item survey was administered by interview for oncologists caring for patients in the study. As part of the study, data were collected regarding the oncologists’ demographic characteristics, the extent of oncologists’ perceived demands on time, and attitudes about end of life/hospice care, uncertainty in patient care, shared care with primary care physicians, and value of supportive care, before oncologists’ patients were accepted into the study. Our findings follow. There were 34 oncologists in the study, 14 from MetroHealth, 19 from the VA, and 1 from both sites. While higher perceived demands on time were predicted to correlate with lower opinions about supportive care interventions, no significant association was found. Significant correlations were found between high perceived demands on time and female gender (p=0.025), as well as between high perceived demands on time and stress about uncertainty (p=0.026). Our findings suggest that stressors on an oncologists’ time may have significant correlations with other stressors such as uncertainty in patient care. These stresses could potentially have a great impact on patient care and decision making, especially in patients facing the end of life in an oncology clinic. Further evaluation is needed to understand this.
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. What was your role in this project?</td>
<td>research assistant/data analysis</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Viruses have evolved mechanisms to counteract host cell anti-viral factors including protein kinase R (PKR), oligoadenylate synthetases (OAS) and short interfering RNAs (siRNA). For example, the vaccinia virus E3L gene and the human cytomegalovirus (HCMV) TRS1 and IRS1 genes bind dsRNA and PKR inhibit the PKR/OAS pathway. Interestingly, the E3L protein also counteracts siRNA mechanisms, most likely binding siRNA and preventing formation of the RNA-induced silencing complex. Recently, two murine cytomegalovirus (MCMV) genes, m142 and m143, were found to encode dsRNA binding proteins which can also block the PKR pathway. Because MCMV is a useful model for studying the pathogenesis of HCMV infections, I designed experiments to determine whether MCMV infection also blocks siRNA function in host cells. I cotransfected a plasmid expressing secreted alkaline phosphatase (SEAP) along with a plasmid expressing an siRNA targeting SEAP (psiRNA-SEAP) into NIH 3T3 cells. Twenty-four hours post-transfection, the cells were mock-infected or infected with MCMV and SEAP activity was assayed twenty-four hours later. I found no significant difference in the knockdown of SEAP activity by psiRNA-SEAP between mock-infected and MCMV-infected cells in several experiments. For example, in one experiment, I detected a 3-fold knockdown of SEAP activity in mock-infected cells compared to a ~4-fold knockdown in infected cells. It remains possible that MCMV might have mechanisms for antagonizing other siRNAs or that function in other cell types or at other stages of infections. However, these preliminary results suggest that MCMV does not block siRNA effects and therefore siRNAs might be useful therapeutic agents against cytomegaloviruses.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Planned and conducted experiments.</td>
</tr>
<tr>
<td>1. Title</td>
<td>Access to Community Services for Children with Special Health Care Needs: Referral Practices and Familiarity with Services of Physicians in Northeast Ohio</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Laura Campbell</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Carolyn Green</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Child Neurology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Rainbow Babies and Children’s Hospital</td>
</tr>
<tr>
<td>7. Support:</td>
<td>none</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD MA</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Seven percent of children in Ohio have special healthcare needs. In addition to complex medical care, these children need community services such as special education, financial assistance, and family support. The goal of this study was to determine in what ways physicians are addressing the community resource needs of their patients: (1) what systems they are using in their practices to coordinate access to community resources; (2) how familiar they are with important community organizations; and (3) what tools would improve resource access for their special-needs patients. A survey was mailed to 282 family practice physicians and pediatricians in the University Hospitals Primary Care Practice network in Northeast Ohio. The response rate was 13.5%. The most common resource coordination systems were: pamphlets/posters available in the office (55%), referrals to social workers (33%), designated office care coordinators (21%), websites (17%), family advocacy programs (11%), and giving phone numbers (11%). Familiarity with important resources varied but was generally lower than expected; only 70% were familiar with the Ohio Bureau for Children with Medical Handicaps, and only 55% were familiar with resources available through the County Board of Mental Retardation and Developmental Disabilities. Respondents were enthusiastic about receiving additional tools to help with community resource coordination — 95% would use a printed list of resources and 87% would use a website. While approaches to coordination of community resource access varied, all survey respondents acknowledged this need and had a system in place to address it. However, a less than 100% familiarity with established community resources suggests that the current system is not adequate for most practices. In response to the survey, we recognize a need to</td>
</tr>
</tbody>
</table>
increase access by formalizing these systems. The most widely suggested tool from the survey was the provision of a web and paper-based database of resource information. As a result we have created a web-based resource directory for Rainbow Babies & Children’s hospital, and will evaluate its impact on resource access and care coordination for children with special health care needs.

| 11. What was your role in this project? | research idea, survey design and coordination, analysis of survey data |
# Title
Epidemiology, Comorbidities, Risk Factors and Treatment Profile of Psoriasis Patients: A Survey/Database Study

## Student Presenter:
Lauren Cao

## Co-workers and Collaborators:
Marjorie Yang, M.D.

## Advisor:
Neil Korman, M.D., Ph.D.

## Departments:
Department of Dermatology

## Institutions:
University Hospitals Case Medical Center

## Support:
Murdough Family Center for Psoriasis (University Hospitals Case Medical Center)

## Please choose your academic program:
MD MS

## What year are you in the program?
2

## Body of Abstract (300 words or less)
Psoriasis is a chronic immune-mediated inflammatory disease with a genetic predisposition that affects around 2% of the U.S. population. Its comorbidities include inflammatory conditions such as CVD, diabetes, arthritis and IBD, which are thought to share common inflammatory pathways with psoriasis. Recent studies demonstrate that psoriasis patients have an increased risk of obesity, diabetes, hypertension, hyperlipidemia and myocardial infarction. Further clinical information from psoriasis patients is needed to identify or confirm associations with other inflammatory diseases, psoriasis risk/protective factors, and treatment response. I had contributed to constructing, revising and administering a comprehensive questionnaire for patients diagnosed with psoriasis. The questionnaire contains 4 sections: 1. Demographic information; 2. Medical, social, family history; 3. Psoriasis/Psoriatic arthritis and treatment history, potential risk/protective factors; 4. Questions regarding psoriasis impact on daily activities and mental health. At least 400 patients, who are 18 years or older and diagnosed with psoriasis, will be enrolled in this study. They will be recruited from UHCMC Dermatology clinical and clinical trials patients, referrals, and website postings. Two study visits are required: 1. Screening visit—patient eligibility is determined, informed consent/HIPAA are administered, questionnaire is given to patient for completion at home; 2. Study visit—completed questionnaire is thoroughly reviewed with patient, patients’ height, weight, bp are measured, psoriatic lesions are clinically evaluated using Psoriasis Area Severity and Index (PASI) and Physician’s Global Assessment (PGA) scores, photos of lesions are taken if necessary. As the data collection phase of the study is still ongoing, there are currently no results. Once the data collection is complete, descriptive analysis will be conducted: prevalence of different
factors will be estimated in univariate and multivariable fashions. The data obtained from the questionnaire could lead to a better understanding of psoriasis, which could be used to improve patients' quality of life and stimulate new studies.

| 11. What was your role in this project? | I contributed to constructing and revising (i.e., questionnaire design), and administering (i.e., data collection) a comprehensive questionnaire for psoriasis patients. |
1. Title  
Examination of HIV Testing Performed According to the CDC's 2001 Guidelines at the MetroHealth System

2. Student Presenter:  
Emma Cermak

3. Co-workers and Collaborators:  

4. Advisor:  
Dr. Ann Avery

5. Departments:  
Infectious Disease

6. Institutions:  
MetroHealth

7. Support:  

8. Please choose your academic program:  
MD

9. What year are you in the program?  
2

10. Body of Abstract (300 words or less)  
Background.  
In 2006, the CDC released recommendations expanding routine HIV testing to include all patients. Previous recommendations released in 2001 called for testing of pregnant mothers and those who engage in "high-risk" behaviors. Studies have shown that once an HIV-positive person learns their status, they take preventative measures, making increased testing an effective means of secondary prevention.

Methods.  
I analyzed all HIV antibody and Western blot confirmatory tests performed on people age 13 years and older at MetroHealth between 2002 and 2006. Descriptive characteristics including gender, age, race, test location, and reason for test were examined. Illnesses appropriate for HIV testing were determined using Medicare-approved ICD-9 codes.

Results.  
There were 37042 tests on 27809 individuals, with 2655 tests on inpatients and 34387 on outpatients. 52.3% of inpatients were male while 70.8% of outpatients were female. The average age of inpatients and outpatients was 40 and 29, respectively. 46.5% of inpatients tested were white, 44.6% were black, and 9.2% were Hispanic. 41% of tests were performed on pregnant women. 7.2% of tests were ordered on people who had an illness often associated with HIV. I was unable to determine the reason for ordering the remaining 52% of tests. The illness-associated tests accounted for 56% of the 303 positive tests, leaving 44% who were identified by targeted testing. The average age of people testing positive was 39.
Conclusion.
More than 50% of patients testing positive were identified using targeted testing according to 2001 recommendations. The mean age of patients testing positive was high at 39 and 50% of patients already had an illness associated with HIV at the time of testing, pointing to a need to expand testing according to 2006 recommendations in order to identify patients earlier in the course of disease, initiate treatment, and prevent the transmission of HIV.

11. What was your role in this project?  
PI
**CHADALAVADA, SEETHARAM**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Title</strong></td>
<td>The Prognostic Value of Peak Oxygen Consumption in Men and Women with Severe Systolic Heart Failure</td>
</tr>
<tr>
<td><strong>2. Student Presenter:</strong></td>
<td>Seetharam C Chadalavada BS</td>
</tr>
<tr>
<td><strong>3. Co-workers and Collaborators:</strong></td>
<td>Eileen Hsich MD, Eugene H. Blackstone MD</td>
</tr>
<tr>
<td><strong>4. Advisor:</strong></td>
<td>Michael S. Lauer MD</td>
</tr>
<tr>
<td><strong>5. Departments:</strong></td>
<td>Cleveland Clinic Lerner College of Medicine of Case Western Reserve University (SC), Departments of Cardiovascular Medicine (EH, MSL, and Cardiothoracic Surgery (EHB) at the Cleveland Clinic Foundation and the Department of Epidemiology and Biostatics, Case Western Reserve University School of Medicine (MSL), Cleveland OH</td>
</tr>
<tr>
<td><strong>6. Institutions:</strong></td>
<td>The Cleveland Clinic Foundation and Case Western Reserve University School of Medicine</td>
</tr>
<tr>
<td><strong>7. Support:</strong></td>
<td>National Institutes of Health grants R01 HL-66004-2, R01 HL072771-01, P50 HL-77107-1 and K12 HD049091-01. The Cleveland Clinic Foundation and Case Western Reserve University.</td>
</tr>
<tr>
<td><strong>8. Please choose your academic program:</strong></td>
<td>MD MS</td>
</tr>
<tr>
<td><strong>9. What year are you in the program?</strong></td>
<td>2</td>
</tr>
</tbody>
</table>
| **10. Body of Abstract (300 words or less)** | Background: Although peak oxygen consumption (VO2) during exercise is frequently used to help predict optimal timing for heart transplantation, its prognostic value in women has not been well defined.  

Methods: We followed for 5 years 2105 adult systolic heart failure patients, including 525 (25%) women who underwent metabolic stress testing between January 1995 and December 2002. Multivariable proportional hazards modeling related VO2 to survival with adjustments for over 30 confounders and with transplantation considered as a time-dependent covariate.  

Results: During follow-up 129 women (26%) died, as did 572 men (36%). There were 175 transplants, including 34 among women. Men and women were similar in age (55 vs. 54 years), but women less likely to have coronary disease (28% vs. 58%). VO2 was strongly predictive of time to death in men (adjusted hazard ratio [HR] for VO2 falling from 15 to 14 ml/kg/min 1.12, 95% CI 1.08-1.16, P<0.0001) and in women (adjusted HR 1.11, 95% CI 1.05-1.18, P<0.0001). There was no gender interaction (P=0.80), but for any given VO2 women were at lower risk (adjusted HR for men 2.22, 95% CI 1.58-3.10, P<0.0001). |
Conclusions: Peak oxygen consumption is a useful tool to predict outcome of systolic heart failure in both men and women. However, for a given VO2 the prognosis in men is worse than for women.
**Impact of Prenatal Brain Injury on the Cerebellum of Adult Rats**

**Student Presenter:** Ryan Chamberlain  
**Co-workers and Collaborators:** Qing Li  
**Advisor:** Dr. Shenandoah Robinson, MD  
**Departments:** Neurosurgery  
**Institutions:** University Hospitals of Cleveland, Case Western Reserve University School of Medicine  
**Support:** T-35 NIH grant  
**Academic Program:** MD  
**Year in Program:** 2  

**Body of Abstract (300 words or less)**

Premature infants often suffer perinatal brain injury that impairs neurodevelopment. Recent research has shown alterations in cerebellar development contribute to observed deficits. After prenatal transient hypoxia-ischemia, infant rats show altered cerebellar development with a preferential loss of neural cells arising at the time of the insult. We propose that alterations observed during cerebellar development will irreparably alter the mature cerebellum. Specifically we predict that excess loss of cell populations arising at the time of the insult will persist into adulthood.

Uterine arteries were occluded for 60 minutes on embryonic day 18, and pups were born at term. Sham controls had surgery without arterial occlusion. Immunolabeling of midline sagittal cerebellar vermis from adult rats was performed. For neurons, anti-calretinin antibodies immunolabeled molecular layer unipolar-brush cells arising at E17-E18. Anti-parvalbumin immunolabeled P15 Purkinje cells and postnatal molecular layer basket and stellate cells. O4 antibodies labeled pro-oligodendrocytes arising at E17-18. Independent observers were blinded to the insult status. Labeled cells from approximately 5 animals from each group were counted. Means were compared using student t-test, with P<0.05 considered significant.

As predicted, a decreased number of unipolar-brush cells that arise around E18 were observed. Purkinje cell numbers were not affected, as they arise before the injury. Basket and stellate cells showed a trend toward decreasing cell number, an unexpected result. These changes may be secondary to damage to the oligodendrocytes or granule cells. Our O4 immunolabeling showed a trend towards decreasing
pro-oligodendrocyte density, similar to loss observed in neonatal rats. Overall, the changes observed in neonatal rats persisted into adulthood, and additional loss of basket and stellate cells occurred.

These findings show that a prenatal systemic insult can alter cerebellar development. A better understanding of the impact of the lesion on brain development will guide the investigations for novel therapy.

| 11. What was your role in this project? | I sliced and immunolabeled the cerebelli then mounted them, performed cell counts, and analyzed the results |
**1. Title**  
In vivo investigation of Dystrophic epidermolysis bullosa in knockout mouse models

**2. Student Presenter:**  
Vincent Chan

**3. Co-workers and Collaborators:**  
Jennifer Remington MD, Julie Burnette

**4. Advisor:**  
Mei Chen PhD, David Woodley MD

**5. Departments:**  
Dermatology

**6. Institutions:**  
University of Southern California

**7. Support:**

**8. Please choose your academic program:**  
MD

**9. What year are you in the program?**  
2

**10. Body of Abstract (300 words or less)**

Dystrophic epidermolysis bullosa (DEB) is an inherited skin disease characterized by chronic blistering and scarring of the skin and mucous membranes. DEB is caused by mutations in the type VII collagen (C7) gene, COL7A1. C7 is the major component of the anchoring fibrils, which are attachment structures located beneath the lamina densa in the epidermal basement membrane zone (BMZ) that mediate dermal-epidermal adherence. COL7A1 gene mutations may result in absent or dysfunctional anchoring fibrils, causing instability within the BMZ and dermal-epidermal separation.

DEB knockout mouse models were used to compare the therapeutic efficacy as well as the immune response of intradermal and intraperitoneal injections of purified recombinant C7 (protein-based therapy) and lentiviral transfer vectors (vector-based therapy). Affected homozygous pups were injected once daily and observed for reduced blister formation and general well-being (i.e. weight). Skin biopsies were taken at different time intervals post-injection. Skin samples were analyzed by H&E staining to verify the presence of intact skin, and immunofluorescence staining, using an antibody to human C7, to detect C7 deposition in the BMZ. Positive human C7 samples were then sent to a collaborator for immuno-EM, which verified restoration of anchoring fibrils.

The intradermal route produced a superior therapeutic response when compared to the intraperitoneal route, judging by phenotypic correction of skin blistering and the amount of BMZ C7-staining. While intradermal protein and lentiviral-based therapy produced similar levels of C7-staining, intraperitoneal protein-therapy was more effective than intraperitoneal
lentivector therapy.

Upon analysis of immune response, it was found that intradermal injections triggered a CD4 response in the dermis within one week of life, while intraperitoneal injections did not elicit a CD4 response until the second week. Anti-human C7 antibody production was verified by ELISA.

<p>| 11. What was your role in this project? | Researcher |</p>
<table>
<thead>
<tr>
<th><strong>1. Title</strong></th>
<th>Spitzoid Tumors of Uncertain Biological Behavior</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2. Student Presenter:</strong></td>
<td>Stephanie F. Chandler</td>
</tr>
<tr>
<td><strong>3. Co-workers and Collaborators:</strong></td>
<td>Mathew W. Ludgate, Timothy M. Johnson, Lori Lowe, Nisha Mierless</td>
</tr>
<tr>
<td><strong>4. Advisor:</strong></td>
<td>Timothy M. Johnson</td>
</tr>
</tbody>
</table>
| **5. Departments:** | 1. Department of Dermatology, Cutaneous Surgery and Oncology  
2. Department of Pathology |
| **6. Institutions:** | University of Michigan |
| **7. Support:** | Crile Fellowship |
| **8. Please choose your academic program:** | MD |
| **9. What year are you in the program?** | 2 |
| **10. Body of Abstract (300 words or less)** | Atypical spitz tumors represent a diagnostically difficult melanocytic tumor which exhibits histopathologic features of both Spitz tumors and Spitz Melanoma. These challenging lesions cannot be differentiated with satisfactory sensitivity and specificity from Spitz Melanoma, and thus the management of and counseling for patients with these lesions—particularly individuals under the age of 18—represents a significant clinical challenge. Characterization of a more substantial number of Spitzoid lesions when combined with long term follow-up data will contribute to the development of guidelines for the care and management of individuals with these challenging lesions. The goal of this project was to determine the biologic behaviors, prognostic factor-risk assessment and predictors of outcome of atypical Spitz tumors. The Multidisciplinary Melanoma Program at the University of Michigan represents the largest program of its kind in the US. Clinical and histopathologic data on patients seen in this clinic with atypical or borderline Spitzoid melanocytic proliferations and Spitzoid Melanomas were identified and reviewed through the ongoing melanoma program database. Relevant cases were abstracted from the database and existing records and analyzed by individuals from pathology, dermatology and biostatistics departments. Cases were analyzed for age at diagnosis, sex, initial tumor diagnosis, surgical action, and adjuvant therapy against their outcome. Results from the initial survey indicated that of 63 patients, 26 were female, 37 were male. Age range was 1-65 years, with the mean age at diagnosis of 23 years. The mean breslow depth reported was 2.26mm. Sentinel lymph node biopsy was performed in 53 patients, 45% of which were positive. 18 of 63 received adjuvant interferon. Positive outcomes for disease free survival for a mean follow-up period of 33 months yielded no recorded mortalities. This study is ongoing with follow up data still being collected, |
but the results will add critical information that may have a significant far reaching impact regarding the optimal management of atypical Spitz tumors in children and young adults.

| 11. What was your role in this project? | Data collection and analysis |
| 1. Title | Assessment of operationalized 3 day-recall of adherence and its association with viral rebound among HIV/AIDS patients receiving antiretroviral therapy at the Special Immunology Unit |
| 2. Student Presenter: | Shelley Chang |
| 4. Advisor: | Ajay K. Sethi, PhD, MHS |
| 5. Departments: | Department of Biostatistics and Epidemiology and Center for AIDS Research (Case Western Reserve University School of Medicine); Special Immunology Unit (University Hospitals Health Systems) |
| 6. Institutions: | Case Western Reserve University |
| 7. Support: | Crile Research Fellowship, Center for AIDS Research (AI036219) |
| 8. Please choose your academic program: | MD PHD |
| 9. What year are you in the program? | 2 |
| 10. Body of Abstract (300 words or less) | Although non-adherence to HAART directly correlates with treatment failure, there is no widely accepted method to assess adherence to HAART in HIV care clinics. Based on prior research, 3-day recall of medication adherence has been operationalized at the SIU, but has not been evaluated. We assessed the correlation of this current adherence measure with viral rebound and adherence to HIV care in this study. Since 2003, 833 patients on HAART have had 4,613 clinic visits in which 3-day recall was assessed at 4,103 (89%) visits for a median of 6 (IQR 3-8) visits per patient. Final cumulative adherence across all visits when adherence was assessed was 100% in 440 patients (55.63%) and <100% in 351 patients (44.37%). Using GEE, there was an association between having <100% cumulative adherence and viral rebound compared to having perfect cumulative adherence [OR=2.80, 95% CI: 1.85, 4.24]. When cumulative adherence was lagged by one clinic visit, the odds ratio remained significant [OR=1.98, 95% CI: 1.33, 2.93], indicating there exists a window of opportunity in which an intervention may improve patient adherence to HAART before the occurrence of treatment failure. When stratifying by level of imperfect adherence, there appeared to be a varying association between level of cumulative adherence and viral rebound. For cumulative adherence levels <50%, 50-70%, and 70-90%, the odds ratios were 4.91 (95% CI: 2.08, 11.62), 5.83 (95%CI: 2.60, 13.09), and 2.37 (95%CI: 1.20, 4.67), respectively, compared to having >90% cumulative adherence. When adherence is lagged, only the 50-70% cumulative adherence stratum remained significant [OR=4.32, 95%CI: 1.80, 10.36]. Significant predictors of rebound were being transgendered, missing clinic |
visits, lower CD4, and longer time since first ARV use. Cumulative adherence is not significantly associated with suppression. Cumulative adherence from operationalized 3-day recall measures appears to be an effective method to predict future viral rebound.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title</td>
<td>Gefitinib resistance and ineffective epidermal growth factor receptor degradation in non-small cell lung cancer cell lines</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Timothy Ting-Han Chang</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Careen K. Tang</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Oncology and Biochemistry</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Lombardi Comprehensive Cancer Center at Goergetown University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Correlating alterations in protein expression levels with Gefitinib (a tyrosine kinase inhibitor) sensitivity promotes further research in finding molecular markers indicative of Gefitinib responsiveness in NSCLC patients. Furthermore, these alterations may also elucidate the pathways by which some NSCLC cell lines are, or become, resistant to Gefitinib, which may aid in the development of more targeted therapies. We hypothesize that ineffective degradation of EGFR may play a critical role in TKI resistance. Several protein expression levels were evaluated using a panel of NSCLC cell lines that include Gefitinib resistant and sensitive EGFR mutant cell lines, a resistant cell line expressing wild-type EGFR, and two unknown phenotype cell lines expressing wild-type EGFR (H596 and H1944) by western blot. Results shows that Gefitinib resistant cell lines have increased expression levels of IGF1Rβ 200 and Sprouty-2 and significantly decreased expression levels of Claudin-7 and FAS in comparison to Gefitinib sensitive cell lines. However, there were no correlations observed in these proteins: ACK, vimentin, Brk, Cortactin, E-cadherin, Survivin, pAkt/Akt, pp44/42, p44/42 and IGF1Rβ 97. Extrapolating the results suggested H596 resistance and H1944 sensitivity towards Gefitinib. Anchorage-dependent growth assays confirmed that indeed, H1944 is sensitive (responds to AG1478 (an TKI) treatments in a dose dependent manner), whereas H596 was resistant (no effect was observed). These results show that alterations in some protein expressions correlate with Gefitinib sensitivity. Our early studies have shown that the Gefitinib resistant cell lines have</td>
</tr>
</tbody>
</table>
ineffective degradation of EGFR. Since Sprouty-2 is involved in the EGFR degradation pathway, immunoprecipitation/immunoblotting was used to elicit the degradation properties of the two unknown phenotype cell lines. Intriguingly, EGFR was efficiently degraded in H1944 whereas the resistant cell line H596 did not effectively degrade EGFR. These results were concomitant with our early findings. Our cumulative evidences show that ineffective degradation is likely to be one of the mechanisms that cause for cellular resistance towards gefitinib.

11. What was your role in this project?  

Researcher
Previous studies have shown the existence of internal clocks in mammalian cardiac tissue which allow for optimized cellular responses to external stimuli. In these studies, metabolic genes – including those regulating carbohydrate utilization, fatty acid oxidation, and mitochondrial function – exhibited diurnal variation with their activity peaking at night. In the setting of pressure overload-induced hypertrophy, however, this diurnal variation was abolished. Thus, a loss of the clock mechanism may be important in the development of left ventricular hypertrophy and systolic dysfunction in the setting of hypertension. To elucidate the role of clock proteins in cardiac remodeling, the present study evaluated the effects of transverse aortic constriction (TAC) on mice with clock and bmal1 deletions. These genes encode transcription factors responsible for induction of other clock-related components. Following the banding procedure, animals were subjected to two-dimensional and Doppler echocardiographic studies for analysis of end systolic and diastolic diameters, relative wall thickness, velocity of circumferential shortening (an index of myocardial contractility), cardiac output, ejection fraction, and fractional shortening. Upon terminal surgery, hearts were harvested and assessed for left ventricular mass, alpha and beta myosin heavy chain content, and atrial natriuretic factor (ANF) expression. The activities of medium chain acyl-CoA dehydrogenase (MCAD) and citrate synthase were measured as an index of fatty acid oxidation and myocardial oxidative capacity, respectively. Additionally, mRNA levels for peroxisome proliferator-activated receptor alpha- (PPARa) regulated genes encoding carnitine palmitoyl transferase-I (CPT-I) and uncoupling protein 3 (UCP3) were quantified using RT-PCR. Finally, plasma free fatty acids and serum insulin concentrations were determined using spectrophotometric techniques.
| 11. What was your role in this project? | Assisting in the execution of experiments, writing |
1. Title
Overview of home care services provided by Jichi Medical University Hospital in Japan

2. Student Presenter:
Samuel Chen

3. Co-workers and Collaborators:

4. Advisor:
Drs. Yuko and Koki Tsuruoka

5. Departments:
Department of Community and Family Medicine

6. Institutions:
Jichi Medical School

7. Support:

8. Please choose your academic program:
MD

9. What year are you in the program?
2

10. Body of Abstract (300 words or less)
The model for primary and family care in Japan has evolved differently from that of the United States as a result of the accessibility of universal health care and cultural differences in familial and societal structure. Long-term care insurance (kaigo hoken) helps to pay for the costs of care for eligible patients through a collective pool maintained by insurance premiums and tax. The development of this system is a reflection of the Japanese emphasis on societal unity and a way to alleviate familial stress that may arise from prolonged elderly nursing care. Through interview and observation of patients receiving long-term care insurance, I was able to construct first an overview of the Japanese home care services provided by Drs. Yuko and Koki Tsuruoka’s team at Jichi Medical University Hospital in Japan. The level of care ranged from health maintenance to terminal care and always involved working closely with the patient’s family and visiting helpers and nurses. Through participant observation, I was then able follow the care of a specific patient, Mr. Y, and aid in the production of an observational study. The study looks at Mr. Y’s weekly home visits, familial obligations and participation in his care, and services provided by external support groups, notably that of a portable bathing service. For bedridden patients such as Mr. Y, having the opportunity to soak in a bathtub greatly improves his quality of life, and must be understood in the cultural context that most Japanese consider a daily soak in the bathtub to be an irreplaceable part of the day. This research project emphasizes the importance of understanding the cultural and societal context of how home care is delivered in Japan.
| 11. What was your role in this project? | Collection of data and observations regarding home care in Japan |
1. **Title**
   Evaluation of Human Beta-Defensin Expression in HIV-Infected Women versus Non-Infected Women

2. **Student Presenter:**
   Silvia Chiang

3. **Co-workers and Collaborators:**
   Ana Vasquez, PhD Candidate (Dr. Miguel Quinones's lab, CCF)

4. **Advisor:**
   Dr. Michael Lederman

5. **Departments:**
   Department of Medicine
   Department of Obstetrics and Gynecology

6. **Institutions:**
   University Hospitals

7. **Support:**
   NIH T35 Grant

8. **Please choose your academic program:**
   MD

9. **What year are you in the program?**
   2

10. **Body of Abstract (300 words or less)**
    Protective mechanisms against HIV acquisition at mucosal sites are incompletely understood. The role of human β-defensins (hBDs), which are antimicrobial peptides, in host defense against HIV is a promising area of study that may illuminate mechanisms underlying disease progression and susceptibility to opportunistic infections. Characterization of hBD-2 and hBD-3 expression in the oral and cervicovaginal epithelia of HIV patients and controls will help define the effects of HIV infection on the expression of these important defenses, as well as elucidate the relationship between defensin levels and mucosal infections such as oral candidiasis, that often complicate HIV infection. Samples will be collected from HIV-infected and non-infected women undergoing routine pelvic examinations. Oral epithelial samples will be obtained by scraping with a plastic loop. Cervicovaginal epithelial samples will be obtained by vaginal scraping for the epithelial cells, and cervicovaginal secretions will be obtained with Sno-strip wicks. Using real-time PCR, this study will compare mRNA expression levels of hBD-2 and hBD-3 between the epithelial cells of HIV-infected vs. non-infected women. Defensin protein levels in cervicovaginal secretions of HIV-infected vs. non-infected women will be measured by ELISA. Messenger RNA and protein expression levels will then be correlated with HIV status, CD4 cell count, and plasma viral load. The Wilcoxon Rank sum test will be used to compare defensin levels between the infected and non-infected groups, and Spearman’s correlations will be used to identify possible associations between defensin levels and clinical variables. IRB approval has been obtained. Collaborators from the Departments of Medicine and Obstetrics/Gynecology have agreed to obtain informed consent and collect specimens from patients. In addition, ELISA and real-time PCR procedures have been developed and tested. The rationale behind this
study and the clinical and laboratory procedures have been presented to
the clinician-researchers of the AIDS Clinical Trials Unit of University
Hospitals.

| 11. What was your role in this project? | project and protocol development, IRB |
Post-operative management of cardiac transplantation requires routine monitoring of allograft rejection. Endomyocardial biopsy (EMB) is currently the gold standard procedure, but is invasive, causes morbidity, and is subject to variability and sampling error. Gene expression profiling (GEP) of circulating peripheral blood mononuclear cells with the AlloMap blood test is a recently-developed alternative for detection of allograft rejection. GEP is accurate, non-invasive, and cost-effective, but the clinical outcomes of using GEP for routine rejection surveillance are still unclear. Therefore, the Invasive Monitoring Attenuation through Gene Expression (IMAGE) study is comparing the event-free survival of heart transplant recipients in their second to fifth year post-transplant using GEP versus EMB for rejection monitoring. Primary events of the study include a decrease in left ventricle function (a decrease in LVEF = 25%); the development of clinically overt rejection (heart failure or hemodynamic compromise); and death (due to any cause). All stable heart transplant recipients in their second to fifth year post-transplant who are at least 18 years old, have a LVEF = 45% (within 6 months), and have coronary artery stenosis < 50% (within 12 months) are approached to enroll in the study. Participants randomized to the GEP arm of the study submit an AlloMap blood sample and an echocardiogram at every routine visit, while patients randomized to the EMB arm submit a biopsy sample, an AlloMap blood sample, and an echocardiogram at every routine visit. As of July 31, 2007, 34 patients were enrolled from the Cleveland Clinic, and 239 patients were enrolled nationwide. However, only 9 primary events had been reported nationwide as of that date. Due to the difficulty in achieving primary endpoints in sufficient time, a data safety monitoring board will review if study should continue with its current protocol. Meanwhile, the
IMAGE study is still in progress.

<p>| 11. What was your role in this project? | Research assistant: helped screen patients, enroll patients, meet with returning study participants, and enter data |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Impact of Socioeconomic Status on Critically Ill Stroke Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Debby Chuang</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Gwendolyn Lynch</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Neurology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>UHHS, CWRU</td>
</tr>
<tr>
<td>7. Support:</td>
<td>T35 Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Background/Objective: Recent studies have supported the notion that lower socioeconomic status is associated with increased stroke risk, greater stroke severity, and poorer overall outcome (1). Our retrospective study set out to determine potential associations between socioeconomic status and the clinical presentation, disease severity, clinical course, and/or discharge status of a single-center population of critically ill stroke patients in the Cleveland, OH area.  

Methods: A retrospective analysis of the 2001 University Hospitals of Cleveland Neurointensive Care (UH-NSU) Hyperglycemia Database was conducted. Subjects were included in the study if the following inclusion criteria were met: age >18 years, admission diagnosis of stroke (cerebral infarction, subarachnoid hemorrhage, and intracerebral hemorrhage), length of stay greater than 24 hours, and available medical records, zip codes, and income category for analysis. The variables included in the analysis were age, sex, race, zip code, past medical history, NSU admission details, NSU vital statistics (blood glucose level, temperature, heart rate, and blood pressure), in-hospital complications, discharge status, and cost of care. The identified zip codes from the data set were used to collect Zip Code Tabulation Areas (ZCTAs) and their associated median family income, median household income, and median non-family income data from the online version of the 2001 US Census database. Once the incomes were categorized into eight $10,000-increments, the patients in our sample were subsequently categorized into their respective income categories through matching zip codes with ZCTAs. Univariate and multivariate statistical analyses were then performed to determine possible associations between the income categories and the stroke patient variables. |
Results/Conclusions: 221 patients admitted for stroke due to cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage were identified and included in the analysis. 90 different zip codes were collected from the patient sample and correlated to ZCTAs. The statistical analysis and other results are pending.


| 11. What was your role in this project? | Research Assistant (Involved in entire project design/development/implementation) |
1. **Title**
   Gentamicin-induced focal lesions in chinchilla vestibular neuroepithelia as defined by calbindin and calretinin immunocytochemistry

2. **Student Presenter:**
   Augustine Chung

3. **Co-workers and Collaborators:**

4. **Advisor:**
   Larry Hoffman

5. **Departments:**
   Division of Head and Neck Surgery

6. **Institutions:**
   University of California, Los Angeles

7. **Support:**
   Crile Fellowship

8. **Please choose your academic program:**
   MD

9. **What year are you in the program?**
   2

10. **Body of Abstract (300 words or less)**
    Gentamicin and other aminoglycosides are known ototoxic agents. The timecourse of hair cell rejection and appearance of apoptotic markers has been characterized previously. Calbindin and calretinin are calcium-binding proteins present in vestibular organs known to distribute across the epithelia of the organs in specific patterns. Hair cells that express calbindin do not express calretinin, and visa versa. Our question was: can focal lesions induced by intraotic administration of gentamicin be defined as calbindin and calretinin immunocytochemistry?

    Gentamicin was administered directly into the right membranous labyrinth of chinchillas during an aseptic surgery. The animals were then kept for different time courses: (1 day, 4 days, 7 days, 10 days, and 4 weeks) before they were sacrificed. The vestibular end organs which were harvested from both sides were the utricles, horizontal cristae, superior cristae, and inferior cristae. The organs were placed in paraformaldehyde overnight, and then whole-mount immunocytochemistry was performed with antibodies against calretinin and calbindin.

    The data set is not complete yet, as the study was ongoing when I left for school. However, before I left, a few things were clear. For one, the left side (which were not injected with gentamicin) served as good controls, as there was no damage. A pattern of damage to the side which was exposed to gentamicin is beginning to emerge. In the utricles, the damage occurs first in the center of the organ and then moves outward. The destruction of calbindin-expressing hair cells and calretinin-expressing hair cells is also exhibiting a non-random time course, but more data is needed before we conclude anything concrete.
11. What was your role in this project? run experiments, analyze data
**1. Title**
Comparing attitudes about, barriers to and intake of vegetables and fruit in participants and non-participants in a program through an urban health care clinic to provides locally grown inexpensive produce

**2. Student Presenter:**
Matthew Clark

**3. Co-workers and Collaborators:**
Elizabeth Jennings, Patricia Mlandenov, Charles Thomas, Denise Kaiser, Sheila McGinty-Kenderes, Maureen Lemieux

**4. Advisor:**
Eileen Seeholzer, MD, MS

**5. Departments:**
- Department of Medicine
- Center for Health Care Research and Policy

**6. Institutions:**
Case Western Reserve University at MetroHealth

**7. Support:**
This project was part of the Adult Weight Management and Health Lifestyles program supported by a century grant from the Saint Luke’s Foundation.

**8. Please choose your academic program:**
MD

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**
Background: Fruit and vegetable consumption is low in poor urban populations and produce costs have increased significantly. Initiatives linking local growers with urban residents improved produce consumption. These programs are not often linked to health centers.

Project Purpose: To measure consumption of, attitudes about and barriers to obtaining fruit and vegetables in enrollees at sign-up and after participation, and in similar non-enrollees, of a program providing local produce through an urban health center.

Methods: Enrollees and a convenience sample of non-enrollees at the health center completed an anonymous written survey with items from the Behavioral Risk Factor Surveillance System (BRFSS) 2003.

Results: Seventy-five non-enrollees and all enrollees (N=29) completed the survey. The fifteen enrollees participating =3 weeks retook the survey in the program’s last month. Enrollees and non-enrollees were nearly all African American (99%) and female (93 and 80%) and had a modal age group of 45-54 years. No enrollees were under age 30. No difference was found between groups in produce consumption, perceived cost or availability of produce, nor perception of cost as a barrier to healthy eating. Over 75% of both groups cited interest to participate in a low-cost produce program. Enrollees were more likely to read nutrition labels and less likely to eat fast food than non-enrollees. At post-participation testing, enrollees reported even less fast food consumption (p<0.0005), otherwise
responses did not differ from pre-participation.

Discussion: High program interest and consistent enrollment support continuation. Efforts to enroll younger patients are needed. The higher likelihood of enrollees to read nutrition labels and lower fast food consumption suggests higher baseline healthy eating behaviors. Post-enrollment surveys did not show increased reported produce consumption, but showed a marked decrease in fast food consumption. Results are limited by small numbers and to an urban older, female African-American population.

11. What was your role in this project?  

Primary co-investigator
1. Title  
Influence of socioeconomic status and sedentary activity on the relationship between body mass index and cardiovascular comorbidities in overweight children

2. Student Presenter:  
Ingrid M. Cobb

3. Co-workers and Collaborators:

4. Advisor:  
Dr. Leslie Heinberg

5. Departments:  
Biostatistics and Epidemiology

6. Institutions:  
Case Western Reserve University School of Medicine

7. Support:

8. Please choose your academic program:  
MD

9. What year are you in the program?  
2

10. Body of Abstract (300 words or less)  
Studies have shown that increased obesity in children is associated with an increased risk of medical co-morbidities. For example, increased BMI is associated with increased cardiovascular risk factors such as for dyslipidemia, hypertension, and glucose impairment. Low socioeconomic status (SES) and increased sedentary behavior are risk factors for the development of obesity.  
Participants (n=163) were enrolled in the Healthy Kids/Healthy Weight (HKHW), which is a clinical research program at Rainbow Babies and Children’s Hospital in Cleveland, Ohio that is dedicated to helping and guiding overweight children and their families build healthy and physical lifestyles. The female to male percentage was 57% to 43%. The participants ages ranged from 4-17, however the largest percent of the participants were in the 10-14 age range. The BMI for the participants were at the 85th percentile which identifies them as at risk for overweight or overweight. This study will examine the possible moderating role of SES and sedentary activity on the relationship between BMI and the risk for cardiovascular factors in a pediatric overweight population. It is hypothesized that lower SES will be related to a greater association between BMI and cardiovascular risk factors. A similar moderating relationship is hypothesized for sedentary behavior.  
Using a linear regression model, SES and sedentary behavior moderated the relationship between the SES and sedentary hypothesis and BMI for the comorbidities of insulin resistance, systolic blood pressure, and triglycerides and BMI. However, the hypotheses were not demonstrated for glucose intolerance, diastolic blood pressure, total cholesterol, LDL, HDL, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia and BMI.
This data represents a possible link to understanding the moderating factors in the role of SES and sedentary activity on the relationship between body mass index and co-morbidities. Future research in this area will further elucidate the factors involved in the increasing medical issue of pediatric obesity.
**1. Title**
Measuring measles virus antibody titers using a flow cytometry-based suspended microsphere assay.

**2. Student Presenter:**
Jeffrey M. Collins

**3. Co-workers and Collaborators:**
Kimmel RJ, Ovsyannikova IG, Vulule J, Poland GA, Moormann AM

**4. Advisor:**
Ann Moormann

**5. Departments:**
(1) Center for Global Health and Diseases, (2) Vaccine Research Group, (3) Center for Vector Biology and Control Research.

**6. Institutions:**
(1) Case Western Reserve University, Cleveland, OH; (2) Mayo Clinic College of Medicine, Rochester, MN; (3) Kenya Medical Research Institute, Kisumu, Kenya.

**7. Support:**
NIH T-35 Training Grant

**8. Please choose your academic program:**
MD MPH

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**
In 2002, the World Health Organization (WHO) estimated 1.4 million deaths in children were due to vaccine preventable diseases. Vaccine coverage has significantly increased since the WHO began the Expanded Program on Immunization (EPI); however, measles accounts for 35% of infant mortality, primarily in sub-Saharan Africa. Immunization coverage is typically measured by the number of doses administered—not by serology. The gold standard for seroconversion is a neutralization assay and ELISA. These methods are costly, time-intensive, not quantitative and require large plasma volumes to test multiple antigens, making the monitoring of immunization coverage by serology impractical. A new flow cytometry-based technology using antigen-conjugated fluorophore-dyed microspheres, referred to as Luminex, has the potential to measure a panel of antibodies using extremely small sample volumes. Immunization coverage continues to improve in Africa; however, the role of immunosuppressive parasitic infections on immunity to EPI vaccines remains unknown. We compared ELISA (BioQuant) to Luminex for measles virus antibody detection in samples from children (2-14 yo) residing in geographically distinct areas of Kenya: Kisumu and Nandi. By IgG ELISA, measles seropositivity was 85% and 62% in Kisumu and Nandi, respectively. A positive threshold was determined for measles-conjugated microspheres resulting in 80% sensitivity and 60% specificity compared to ELISA. When dichotomized by site and age the sensitivity increased for younger malaria-exposed children. Low seroprevalence could be due to lack of vaccine coverage or vaccine failure. In order to further optimize and validate Luminex to measure measles virus antibodies the history of measles immunization and...
measles-associated illness are being collected on this cohort of children. Longitudinal repeat cross-sectional samples will determine if measles antibodies wane or are associated with malaria. A quantitative measure of measles-induced antibody titer has the potential to address the impact of malaria on measles vaccine efficacy.

| 11. What was your role in this project? | I performed the laboratory experiments and the data analysis. |
Obstructive sleep apnea (OSA) is a growing problem currently affecting more than one in five Americans. A variety of treatments are used to treat OSA including positive air pressure, radiofrequency and laser ablations, and Uvulopalatopharyngoplasty. These techniques primarily focus on removing or destroying tissue in the back of the tongue or surrounding structures, reducing their thickness, and thereby enlarging the airway. Our study aims at developing a non-invasive laser ablation protocol under magnetic resonance (MR) imaging guidance to accurately, and reproducibly diminish the tongue base. This pilot uses four 75-100lb pigs that were scanned using T1-weighted TSE, T2-weighted TSE, STIR, and TrueFISP 3D sequences. After preliminary scans, the ablation was made using a diffusing tip laser fiber guided under MRI through the skin and platysma muscle into the median sagittal plane between the lingual arteries in the posterior tongue base. The tip was advanced to a point just below the mucosa. A Nd:YAG laser set at 19W was applied for six minutes to generate an average lesion of 21.9±4.2cm³. The same MRI sequences were performed immediately following, at two weeks, one month, and 2.5 months. The data was imported into commercial software and measurements were made of the lesion length, width and height; the thickness of the tongue around the lesion; and the volume of the lesion. The lesion, at 2.5 month follow up, was 10.0±8.3% of the original. In one month, a statistically significant decrease in tongue thickness (p=0.025) was recorded and again at 2.5 months (p=0.05). Tongue base thickness decreased an average of 0.6±0.5cm (~15%) in thickness at one month, and 0.5±0.3cm (~15%) at 2.5 months. These results have shown a measurable and statistically significant decrease in tongue base thickness. Further results will focus on the...
longer-term outcome and will increase the statistical significance of these measurements with additional animals.

| 11. What was your role in this project? | Assisted with procedure, Performed data analysis |
Pc 4 Binding to Cardiolipin: A Study in Liposomes

2. Student Presenter: Grace B. Delos Santos

3. Co-workers and Collaborators: Dr. Myriam E. Rodriguez

4. Advisor: Dr. Nancy L. Oleinick

5. Departments: Radiation Oncology

6. Institutions: Case Western Reserve University


8. Please choose your academic program: MD

9. What year are you in the program? 2

10. Body of Abstract (300 words or less) Porphyrins and related macrocycles are currently employed as photosensitizers in photodynamic therapy (PDT), which is a non-invasive and highly specific cancer treatment modality that uses singlet oxygen to exert cytotoxic effects on cells. Cells that have been treated with PDT have been shown to undergo apoptosis or necrosis, although the initiating events of apoptosis that are unique to PDT have yet to be elucidated. Pc 4, a phthalocyanine photosensitizer first synthesized at Case and now in clinical trial at University Hospitals, has been shown to bind preferentially to mitochondrial membranes and to exert photodamage to certain membrane molecules. Cardiolipin (CL) is a major phospholipid in the mitochondrial inner membrane. Fluorescence resonance energy transfer (FRET) studies have shown colocalization of Pc 4 and cardiolipin in the mitochondrial membrane, which points to CL as a possible binding site and target site for Pc 4. Herein are reported the binding constants of Pc 4 in liposomes of increasing cardiolipin content. Unilamellar liposomes were used as membrane models to test the incorporation of the dye. It was shown that Pc 4 does not display preferential binding to cardiolipin. Moreover, binding affinities appear to be independent of the lipid composition of the liposomes. The behavior of the Pc 4 analogues, Pc 181, Pc 12, and Pc 135, was also investigated in liposomes; each contains two alkyl-siloxy ligands linked axially to the central silicon in contrast to Pc 4, which has one such ligand. Each displayed a higher binding affinity than did Pc 4 due to a greater extent of disaggregation. Nonylacridine orange (NAO), a molecule reported to preferentially bind to cardiolipin, did not display preferential binding to cardiolipin in the
liposomal system. This does not preclude cardiolipin as a binding site for Pc 4 but rather suggests that the binding affinity is system dependent and that the liposomal system is better at detecting differences in disaggregation over differences in binding affinities.

<p>| 11. What was your role in this project? | Performance of experiments; experimental design; interpretation of data |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Neural Substrates of Age-related Decline in Executive Functions: In vivo measures of gray-matter and white-matter abnormalities from magnetic resonance imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Deng, Min</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Bakkour A, Dickerson, BC</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dickerson, BC</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Martinos Imaging Center</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>MGH; Harvard Medical School; Boston, MA</td>
</tr>
<tr>
<td>7. Support:</td>
<td>MSTAR fellowship (M.D.) and NIH grant K23-AG22509</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less)           | Background: Executive functions are cognitive abilities that include planning, decision-making, mental flexibility, mental processing speed, working memory, and elements of controlled memory retrieval. These abilities are fundamental for independent function in daily life, and are well-known to be impaired in a variety of neuropsychiatric disorders, including Alzheimer’s disease, ADHD, and schizophrenia, among others, as well as in normal aging. Yet there is a major gap in our knowledge of the anatomical substrates associated with executive functions. With the projected increase in population of elder adults (>65 years old) in the U.S. from 40 million in 2010 to 86+ million in 2050, there is an increasing need to understand the neural substrates of executive function with the hope of preventing executive dysfunction.  

Objectives: The purpose of this study was to investigate the decline of executive functioning in healthy older adults (>65 years old). We hypothesized that there would be evidence of gray-matter cortical thinning as well as loss of white-matter integrity in neuro-anatomical regions associated with executive functioning in the elderly.  

Methods: This study was done with an existing database of 37 normal elder adults who had undergone a series of neuropsychological evaluations, structural MRI, and DTI scans. Subjects were excluded if they had an axis I psychiatric disorder, cerebrovascular disease, Alzheimer’s disease, or any disorder which could affect normal cognitive function. Structural MRI and DTI scans were obtained with a high-resolution Siemens Avanto 1.5T MRI scanner. Cortical thickness measurements were determined using FreeSurfer, and DTI. |
measurements were obtained using FreeDiffusion, both developed at the Martinos Center (Boston, MA). Regions of interest (ROI) in the frontal and parietal lobes were selected a priori based on previously published literature. Correlational analyses were performed between these ROI and performance on the following neuropsychological tests: Trail Making Test and Verbal Fluency Test.

| 11. What was your role in this project? | Study design, literature search, data analysis, cortical measurements, statistical analysis |
**DERAKHSHAN, JAMAL**

1. **Title**
   Inversion-optimized, multi-slice, parallel TOSSI (T-One insensitive Steady State Imaging)

2. **Student Presenter:**
   Jamal Derakhshan(1)

3. **Co-workers and Collaborators:**
   M. Blaimer(2), P. Schmitt(3), J.L. Sunshine(2), J.L. Duerk(1,2), M.A. Griswold(2)

4. **Advisor:**
   Jeff Duerk, Ph.D.

5. **Departments:**
   (1)Department of Biomedical Engineering  
   (2)Department of Radiology  
   (3)MRI

6. **Institutions:**
   (1)Case Western Reserve University  
   (2)University Hospitals of Cleveland and Case Western Reserve University  
   (3)Siemens Medical Solutions, Erlangen, Germany

7. **Support:**
   NIH T32 GM07250-Case MSTP  
   Siemens Medical Solutions-MRI

8. **Please choose your academic program:**
   MD PHD

9. **What year are you in the program?**
   4

10. **Body of Abstract (300 words or less)**
    The spin-spin relaxation time (T2) of tissue is of great clinical importance for diagnosing diseased tissue from its healthy counterpart. Currently it takes 1.5 minutes to generate a T2-weighted (T2W) brain scan using a Turbo Spin-Echo (TSE) pulse sequence. Recently, a new pulse sequence called TOSSI (T-One insensitive Steady State Imaging) has been developed which is an alternative way of generating T2 contrast. This is a steady state free precession (SSFP) based MRI pulse sequence which has an inherently high signal-to-noise ratio. Pure T2 contrast is generated by non-uniformly spaced inversion pulses which align the bulk magnetization in states parallel and anti-parallel to the main magnetic field in a way that negates the T1 relaxation effect. The two previously published studies using TOSSI were limited to non-optimal inversion timing and to single-slice acquisitions. In this work we engineered several improvements into the TOSSI pulse sequence such as better image contrast, higher spatial resolution at a fixed echo time, and the ability to perform multi-slice acquisitions. We show that TOSSI can be used to obtain rapid multi-slice T2W images of the head in ~0.8 sec/slice or 16 seconds for a complete brain scan. We were able to obtain T2W brain images in a moving human subject without the need for additional motion correction; something not achievable with a TSE sequence. We also show that TOSSI is able to generate better T2W brain scans compared to other fast T2W pulse sequences such as HASTE and spin-echo EPI.
Introduction
In diseases such as atherosclerosis, it is necessary to accurately depict the blood vessel wall for the diagnosis of pathology and for vascular interventions such as angioplasty and stent placement. A startup company specializing in devices for MRI (Interventional Imaging Inc., Cleveland, OH) has developed a 5 French disposable catheter for imaging the vessel wall using MRI. The aim of this study was to assess the catheter sensitivity in phantom experiments and to test the ability to actively track and image arteries in vivo.

Methods
All experiments were performed in a new 1.5 T interventional MRI scanner (Magnetom Espree, Siemens Medical Solutions, Erlangen, Germany). The catheter was placed in a tub of doped water and high resolution/small field-of-view images were acquired. In 13 healthy, 100 pound, anesthetized pigs, the catheter was introduced though a sheath in the femoral artery. The catheter was advanced under real-time MRI guidance to the femoral, iliac, subclavian and carotid arteries using the Interactive Real Time Tip Tracking pulse sequence (Siemens Medical Solutions, Chicago, IL). Once at the targeted vascular locations, images of the vessel wall were acquired using the catheter.

Results
In phantom experiments the catheter sensitivity was determined to be 1-2 cm axially and 2 cm longitudinally. In vivo, it was possible actively track the catheter to the targeted locations. The catheter was able to access
medium sized arteries (as small as 3 mm). The catheter had a sensitivity radius of 1 cm in vivo. Images with 160 µm in-plane resolution and 5 mm slice thickness were acquired. Using these images it was possible to differentiate the vascular lumen, the vessel wall as well as surrounding tissue.

Conclusion
The new 5 French catheter can be actively tracked to targeted anatomy and can be used to generate high resolution vessel wall images in vivo.

11. What was your role in this project? MRI Pulse Sequence Development, Data Acquisition, Data Analysis, Oral Presenter at 6th Interventional MRI Symposium (Leipzig, Germany)

1. Title A New Method of Supressing Blood Flow Signal in MRI

2. Student Presenter: Jamal J. Derakhshan

3. Co-workers and Collaborators:

4. Advisor: Jeffrey L. Duerk

5. Departments: Biomedical Engineering and Radiology

6. Institutions: Case Western Reserve University and University Hospitals Case Medical Center

7. Support: NIH T32 GM007250 and Siemens Medical Solutions - MRI

8. Please choose your academic program: MD PHD

9. What year are you in the program? 6

10. Body of Abstract (300 words or less) Atherosclerosis is a debilitating and deadly disease which is estimated to affect 4.6 million people in the United States alone. Magnetic Resonance Imaging (MRI) with attenuated signal from flowing blood (dark blood MRI) can enhance depiction of pathologies involving the great vessels such as atherosclerosis. Current steady state dark blood TrueFISP techniques lead to a doubling or more of imaging time. We developed a new way of generating steady state dark blood MRI contrast in a fast, high signal-to-noise ratio TrueFISP sequence. Computer simulations were developed and used to determine the theoretical effect of the proposed technique on stationary and moving spins. Phantom experiments involving doped water bottles and tubes with flowing water at different physiologically relevant speeds were used to simulate stationary tissue and flowing blood, respectively, and to quantify actual flowing spin signal suppression. In vivo human images using regular TrueFISP (control) and
the newly developed dark blood technique were acquired and used to
determine in vivo flow suppression and stationary tissue effects. Good
flow suppression over the velocity ranges simulated and tested in
phantoms was observed. For example, the simulation results for flowing
spins with velocity = 25 cm/s predicted that > 95% suppression could be
achieved. While stationary spin signal loss would be 24.3%. Importantly,
the flowing spin signal to stationary tissue signal ratio could be reduced
from 1.76 to 0.09 using the new technique. Phantom results corroborated
the simulation results with actual flow suppression > 95% and stationary
spin losses of ~ 25%. Human in vivo imaging results demonstrated the
ability to suppress both through plane and in plane blood flow as well as
the losses in stationary tissue. These studies demonstrate theoretically
and experimentally that the steady state signal from blood flow can be
suppressed in a TrueFISP sequence without lengthening the repetition
time.

| 11. What was your role in this project? | My idea. I developed the simulation code, programmed the imaging sequence, collected the data and did the analysis |
Title: Has PSA-Induced Stage Migration Ended?

Student Presenter: Fei Dong

Co-workers and Collaborators: Alwyn M. Reuther, Cristina Magi-Galluzzi, Ming Zhou, Patrick A. Kupelian

Advisor: Eric A. Klein

Departments: Glickman Urological Institute, Taussig Cancer Center, Department of Anatomic Pathology (CCF); Department of Radiation Oncology (MDA Orlando)

Institutions: Cleveland Clinic Foundation, M.D. Anderson Cancer Center Orlando

Support: None

Academic Program: MD

Year in Program: 2

Body of Abstract (300 words or less)

Purpose: Serum prostate-specific antigen (PSA) screening has led to pathologic stage migration. We examined patients treated by radical prostatectomy between 1987 and 2005 to establish temporal trends in rates of extraprostatic extension (EPE), organ-confined disease (OC), and clinically insignificant disease.

Methods: Surgical pathology of 3364 patients treated consecutively at a single institution was analyzed for EPE and OC. In addition, 2256 specimens removed between 1999 and 2005 were evaluated for clinically insignificant disease (tumors < 0.5 cc, surgical Gleason grade < or = 6, and no EPE). Trends were statistically evaluated from 2005 to the earliest year at which the Cochran-Armitage Test was not significant, using Bonferroni’s adjustment with cutoff of p = 0.0029.

Results: From 1987 to 2005, pathologic staging showed a decreasing trend for EPE and increasing trend for OC (both p < 0.0001). There was no trend in the proportion of EPE (p = 0.025) or OC (p = 0.007) from 1998 to 2005. The proportion of clinically insignificant disease showed no trend for the entire period for which data was available, from 1999 to 2005 (p = 0.829).

Conclusion: Trends of pathologic stage migration of the early PSA era have diminished since 1998, while the proportion of clinically insignificant disease remained constant. These findings suggest that the reservoir of undetected prostate cancers may be depleting, and that PSA-associated pathologic stage migration has plateaued. The current rate of detection may more accurately reflect the true incidence of disease.
### 11. What was your role in this project?
I analyzed results, drew conclusions, and wrote the manuscript with appropriate literature reference. The manuscript is currently in the process of submission to the Journal of Urology.

### 1. Title
Kruppel-Like Factor 2 and the Endothelial Response to Oxidative Stress

### 2. Student Presenter:
Fei Dong

### 3. Co-workers and Collaborators:
Zhiyong Lin and Mukesh K. Jain

### 4. Advisor:
Mukesh K. Jain

### 5. Departments:
Cardiovascular Research Institute

### 6. Institutions:
Cleveland Western Reserve University

### 7. Support:
NIH T35 Award in Heart, Lung, Blood, and Sleep Disorders

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
3

### 10. Body of Abstract (300 words or less)

**Purpose**
Reactive oxygen species mediate a wide range of effects in human endothelial tissue and are suspected to contribute to the pathogenesis of vascular diseases, including atherosclerosis. We aim to define the significance of KLF2, a transcription factor that confers anti-inflammatory properties to the endothelium, in mediating the endothelial response to oxidative stress.

**Method**
KLF2 overexpression in primary human umbilical vein endothelial cells (HUVECs) is achieved by adenovirus-mediated gene transfer. Following treatment with peroxides, HUVEC morphological and biochemical responses are characterized.

**Results**
In response to acute oxidative stress, HUVECs undergo dramatic and reversible morphological changes, including cell shrinkage, membrane blebbing, and cell-cell dissociation. These changes are completely suppressed by KLF2 overexpression, possibly through the activation of classic ROS-signaling pathways, ERK and JNK.

**Conclusions**
Exogenous KLF2 overexpression strongly suppresses the endothelial
response to acute oxidative stress. The physiological significance of this observation remains to be elucidated.

<p>| 11. What was your role in this project? | We initiated this project to explore any connection between KLF2 and endothelial oxidative stress. I performed experiments and analyzed results. |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Interactions between mycobacterial lipoproteins and Toll-like receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Michael G. Drage</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Clifford Harding</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Pathology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>4</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Mycobacterium tuberculosis (Mt) causes chronic infection in otherwise healthy individuals. We have hypothesized that the ability of Mt to decrease antigen processing and presentation by the host cell is one mechanism that enables Mt to survive within the macrophage. This effect by Mt is dependent on the presence of Toll-like receptor (TLR) 2. We have isolated several mycobacterial lipoproteins that signal through TLR2 and inhibit antigen processing and presentation. TLR2 is thought to signal as a heterodimer, paired with either TLR1 or TLR6. Bioassays using cells derived from TLR1 or TLR6 deficient mice suggests that TLR2/1 heterodimers bind triacylated lipoproteins and TLR2/6 heterodimers bind diacylated lipoproteins. Recent studies by our group and others suggest that there may be other ligand characteristics that influence signaling requirements by lipoproteins. The goal of this study is to examine the TLR2 heterodimer binding requirements of Mt lipoproteins using both an in vitro bioassay using TLR deficient murine macrophages and human TLR fusion proteins.</td>
</tr>
</tbody>
</table>
Exercise testing is regularly used for both understanding levels of performance in athletes, as well as diagnosing cardiopulmonary disease that becomes apparent under physical stress. Our research aims to study the dynamics of oxygen delivery and utilization at the onset of exercise under normoxic and hypoxic conditions to determine what adaptations are made by training to oxygen uptake and delivery dynamics, and to develop a model to predict what changes occur to oxygen delivery at and within muscle tissue. Our hypothesis is that cardiac output is not the limiting factor in sub-maximal exercise onset. We intend to elucidate what aspects of oxygen delivery are rate limiting in the immediate response to exercise. To examine this window of time at exercise onset, subjects exercised under light and heavy workloads determined as a percent of maximal effort achieved during a ramp test under both normoxic and hypoxic conditions. In order to determine the dynamics of oxygen uptake and utilization the following parameters are measured: blood pressure, heart rate and rhythm, oxygen consumption from the expired air, muscle oxygenation using NIRS, stroke volume and cardiac output, systemic pO2 and pCO2 using a thermal probe, hemoglobin oxygen saturation, and finally an estimation of thigh volume is made. Data collected and analyzed during the summer was incomplete due to the 8-week training regimen that the subjects must complete; however, preliminary results showed promising progress towards establishing each system’s individual rate of response. Data was plotted and curve fitting performed using published models for exercise dynamics to establish coefficients corresponding to the rate of system response. In conclusion further work is necessary for collection of data and analysis. All aspects of the study are progressing at an expected pace, with further analysis we expect to determine what are
the rate limiting factors in immediate exercise response.

| 11. What was your role in this project? | Data Collection and Analysis |
1. **Title**
   Distinct patterns of gene expression in androgenetic and senescent alopecia: a microarray-based study

2. **Student Presenter:**
   Yevgeniya Dvorkin

3. **Co-workers and Collaborators:**
   P Mirmirani, S Oshtory, TS McCormick, KD Cooper and P Karnik

4. **Advisor:**
   Pratima Karkink, Ph.D

5. **Departments:**
   Department of Dermatology

6. **Institutions:**
   University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH

7. **Support:**
   North American Hair Research Society
   Cicatricial Alopecia Research Foundation
   Dermatology Foundation
   Skin Diseases Research Center P&F grant to PK

8. **Please choose your academic program:**
   MD

9. **What year are you in the program?**
   2

10. **Body of Abstract (300 words or less)**
    Androgenetic (AGA) and senescent alopecia (SA) are the two most common non-scarring alopecias. Although the histopathology of both disorders involves follicular downsizing, the differences in the age of onset, pattern of hair loss and hormonal involvement suggest a diverse etiology and mechanism(s) of pathogenesis. To understand the molecular disease mechanisms, we analyzed gene expression profiles of scalp tissue biopsied from three groups of men aged 60 and older. Group 1 (Controls, n=8, pooled) included men with no visible hair thinning. Group 2 (SA, n=8, pooled) included men with no visible hair thinning in their 20's, 30's and 40's. Group 3 (AGA, n=8, pooled) with hair thinning established to have occurred prior to age 40. Affymetrix Human-U133B 2.0 oligonucleotide GeneChips were used to search for significant alterations in scalp biopsies. Expression data was first obtained and analyzed with GCOS and GeneSpring. In AGA, we observed downregulation of genes involved in anagen onset (Wnt-β-catenin, TGF-α, TGF-β, Stat-3, Stat-1), epithelial signal to dermal papilla (PPARδ, IGF-1), differentiation of hair shaft (Notch, Msx2, KRTs, KAPs) and anagen maintenance (Msx2, Activin, IGF-1). The upregulated genes were involved in catagen (BDNF, BMP2, BMP7, VDR, IL1, ER) and telogen induction and maintenance (VDR, RAR). In contrast, the transcriptional profile of SA was very different. Downregulated genes were involved in actin cytoskeletal dynamics (DST, ACTN2, TNNI3, and PARVB), energy metabolism and mitochondrial function (JAK2, PRKD3, AK2, TRAP1, TRIO, ATP12A, MLL4, STK22B). The upregulated genes involved oxidative stress and inflammatory response genes. In AGA, molecular signals required for
anagen onset and maintenance are downregulated and catagen inducers are upregulated causing follicular downsizing. In contrast, follicular downsizing in SA is the result of loss of communication between the dermal papilla and the stem cells of the bulge region required for anagen onset. The molecular profiles of AGA and SA are very different suggesting that they are two distinct disorders.

| 11. What was your role in this project? | data analysis and organization |
1. Title | Prevalence of Smoking Cessation Counseling at a Public Inner-city Hospital
---|---
2. Student Presenter: | Teresa M. Edwards
3. Co-workers and Collaborators: | N/A
4. Advisor: | Dr. John Daryl Thornton
5. Departments: | Pulmonary and Critical Care
6. Institutions: | Case Western School of Medicine
| MetroHealth Medical Center
7. Support: | NIH Heart, Lung and Blood Fellowship
8. Please choose your academic program: | MD
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | Background: Several studies have documented the effectiveness of inpatient smoking cessation counseling in a trial setting, but few have documented how often this occurs or its effectiveness in clinical practice.

Methods: We interviewed 77 consecutive patients who had been admitted for at least 48 hours into a public inner-city hospital. Patient demographics and smoking status were ascertained, and patients were asked whether they were counseled to quit by their current providers, and their willingness to quit. Medical records were reviewed to determine which providers documented smoking status, whether nicotine replacement therapy (NRT) was prescribed, and whether cessation clinic referrals were made. Patients were called one week following discharge to determine change in smoking status.

Results: 33 patients (43%) were current smokers and 20 (26%) former smokers -- all 53 had smoking-related comorbidities. Of the 33 currently smoking patients, the average pack-years was 27+/−26. Smoking status was documented by ER staff for 9 (27%) patients, admitting nurse for 29 (88%), resident for 21 (64%) and attending for 6 (18%). Only 10 (30%) patients were counseled to stop smoking; 6 (18%) were counseled by a physician. None were offered NRT, and only 9 (27%) were referred to a ambulatory smoking cessation program. However, 21 (64%) desired aid with quitting. One-week post discharge, 3 more had been offered NRT or counseling prior to discharge, but 8 (24%) had subsequently quit spontaneously citing concerns about their health.

Conclusions: In this ongoing study, smoking status of inpatients was quite prevalent but variably assessed. Among smokers, few were offered...
cessation therapy despite expressing a desire to quit. Further work is needed to determine the factors associated with inpatient smoking assessment and intervention.

| 11. What was your role in this project? | Wrote research proposal, designed data collection tool, administered surveys, reviewed patient charts, and conducted follow-up phone calls |
**Body of Abstract (300 words or less)**

Objectives: Little data exists on relationships between acculturation and healthcare beliefs regarding the nature of healthcare itself and medical encounters. Elucidating these relationships may contribute to improved understanding in minority population doctor-patient relationships and may also improve cultural competency.

Methodology: I collected survey data from 342 subjects from outpatient clinic areas in an urban public hospital. I developed a 16-item survey that included 6 demographic and socioeconomic items and 10 health belief items. These latter items assessed patients’ opinions and beliefs about the nature of healthcare (response options strongly disagree, disagree, neutral, agree, strongly agree) healthcare is a right, a privilege, should be ensured by government, etc.,) and physician relationships (doctor takes my concerns seriously, charges too much, etc.). Acculturation was dichotomized--more/less acculturated--and operationalized by interview language--English or Spanish-speaking, respectively. I provide 1) descriptive statistics of demographic, socioeconomic, and health belief items; 2) psychometric properties of health belief items stratified by acculturation.

Results: English-speaking respondents (n=186) were younger, had higher education levels, and were more likely insured compared to their Spanish-speaking counterparts (n=156). Spanish-speakers responded significantly more positively to the following: doctors charge fair prices; people should be personally responsible for obtaining healthcare; healthcare is a privilege. In contrast, English-speakers responded significantly more positively to the following: healthcare is a right, government should ensure healthcare. Factor loadings differed, as well.
The average inter-item covariance was 0.13; scale reliability coefficient was 0.61.

Discussion: Spanish and English-speakers have significantly different views on health care in several areas. I originally hypothesized that Spanish-speakers would be more likely to view healthcare as a right and something that government should ensure; however, the data suggests English-speakers are more likely to hold these views. These differences may be explained by a stronger sense of entitlement among the English-speakers compared to Spanish-speakers.

11. What was your role in this project?

Lead investigator
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Physiologic properties of CMP1458 in rabbit vascular tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Uchenna Emeche1</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Chukwuemeka Nwokocha2</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Anthony Ebeigbe2</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Physiology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>1Case Western Reserve University School of Medicine, Cleveland, Ohio 44106 2Department of Physiology, Faculty of Medical Sciences, University of Benin, Edo State, Benin City, Nigeria</td>
</tr>
<tr>
<td>7. Support:</td>
<td>National Institutes of Health and the Minority Health International Research Traineeship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Pyrenacantha staudtii leaves are widely used in West Africa to treat dysmenorrhea, intestinal colic, and threatened abortion. 3-carbomethoxypyridine (CMP1458), the crude methanolic fraction of the plant extract, has a relaxant effect on uterine smooth muscle, promoting relaxation of both spontaneous and oxytocin-induced contractions. However, its effects in other body tissues have yet to be elucidated. Our research aims to determine the physiologic properties of CMP1458 in the systemic vasculature through experimentation with rabbit carotid artery. Two-millimeter segments of rabbit carotid artery were hung in an organ bath under 1g of tension. Viability testing was performed prior to each experiment using phenylephrine to induce contractions. Only tissues producing an appropriate response to viability testing were used for further experimentation. To determine CMP1458 activity, a dose response curve was performed. The results demonstrated dose-dependent, opposing actions of CMP1458. At final bath concentrations less than 10-7M, vasodilatory activity prevailed. However, at higher concentrations, vasoconstriction persisted. There are several hypotheses to explain these findings. It is possible that at lower concentrations, receptor(s) for CMP1458 may not be saturated. While, at higher concentrations, receptors for CMP1458 may be saturated allowing CMP1458 to serve as ligand for another, structurally similar receptor that promotes vasoconstriction. Also, at higher concentrations, receptors may be downregulated so that the vasodilatory effects are lost. Lastly, CMP1458 may act as an agonist at</td>
</tr>
</tbody>
</table>
lower concentrations and an antagonist at higher concentrations.

The research project is currently directed at determining the source of CMP1458 activity, whether endothelium-induced or endothelium-independent. This will facilitate the discovery of the mechanisms of action. The exposition of the mechanisms of action of both effects is vital to determine whether the extract has any additional pharmaceutical potential and determine the existence and mechanism of adverse effects, which may be affecting those currently using the leaf for treatment.

11. What was your role in this project?

Performance and analysis of experiments, writing abstract
Background:
The focus of previous research on improving follow-up of abnormal Pap smears has been on low-income, minority women in urban, academic settings. However, follow-up rates of middle income women are between 50 – 70% and represent an important missed opportunity to prevent the progression of cervical cancer. This study was designed to evaluate a simple, yet systematic office reminder and tracking program in the setting of a suburban family practice and its effectiveness at improving the rate of follow-up of abnormal Pap smears.

Methods:
A retrospective chart review was conducted in a single suburban Family Medicine practice in Northeast Ohio. Sixty-five women with abnormal Pap test results were studied, 37 pre-intervention and 28 post. The main outcomes of interest were rate of adherence to recommended follow-up and delay in follow-up.

Results:
Overall, adherence to recommended follow-up during this time period was 92.1 %. There was no significant difference in follow-up rates detected after the implementation of a systematic reminder program; however there was a trend toward decreased delay in follow-up subsequent to the intervention (7.1 % vs. 24.3 %, p = 0.533). Of those receiving follow-up, 19.6 % were delayed, taking more than 3 months past the recommended follow-up to receive care. Patients with lower grade abnormalities were more likely to receive delayed follow-up care, while those who received a recommendation for colposcopy were less likely to have a delay in follow-up. Final collection of outcome measures for 14 cases is currently in progress and will be complete by presentation date and incorporated.
Conclusions:
A simple reminder system that requires few resources can have a significant impact on the follow-up of abnormal test results. Busy family physicians can use this model as evidence for application in their own practices.

| 11. What was your role in this project? | Project idea, development, and implementation including data collection and analysis |
1. Title: The Vestibulo-Ocular Responses in Progressive Supranuclear Palsy

2. Student Presenter: Igor E. Estrovich

3. Co-workers and Collaborators: Ke Liao

4. Advisor: R. John Leigh

5. Departments: Departments of Neurology and Biomedical Engineering

6. Institutions: Veterans Affairs Medical Center

7. Support: Supported by NIH grant EY06717, the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, and the Evenor Armington Fund.

8. Please choose your academic program: MD

9. What year are you in the program? 2

10. Body of Abstract (300 words or less)

PSP patients suffer from a high rate of falling early in the progression of the disease, and this tendency is a leading cause of morbidity. However, in contrast to the epidemiology and clinical sequelae of falling episodes, the underlying pathophysiology of why patients fall is not a completely solved body of knowledge. This study attempted to isolate the specific impairment of the vestibular reflexes that cause this propensity to fall. These experiments demonstrate that the angular vestibulo-ocular reflex (aVOR), which depends on the labyrinthine semicircular canals, is intact in PSP, while the translational vestibulo-ocular reflex (tVOR), which depends on the otoliths, is impaired. We measured eye rotations induced by horizontal head-and-body rotations (yaw) or vertical translations (bob), and combination of the two in five PSP and 15 control subjects. Subjects viewed small targets located either at 2 m or 15 cm while their eye movements were measured using the magnetic search coil technique and head movements were measured by infrared reflectance method. Control subjects showed increased gain of aVOR and tVOR during viewing of a near versus far target, as dictated by geometric factors. PSP patients showed an appropriate modulation of aVOR gain during near viewing, but a deficient tVOR during all viewing conditions. This study presents evidence that, in PSP, there is selective failure of translational vestibular ocular responses which sense linear accelerations, while angular vestibular ocular reflexes are preserved. Whereas this deficit in otolith vestibular ocular reflexes provides insight into the pathology of PSP, further experimentation is needed to determine if there is a corresponding deficit in the otolith-spinal reflexes, which are ultimately responsible for the falls.
| 11. What was your role in this project? | Research Assist |
| 1. Title | Anxiety Experienced by Parents in a Multi-bed Neonatal Intensive Care Unit |
| 2. Student Presenter: | Emily Farrin |
| 3. Co-workers and Collaborators: | |
| 4. Advisor: | Michele Walsh, M.D. |
| 5. Departments: | Neonatology |
| 6. Institutions: | Rainbow Babies and Children’s Hospital |
| 7. Support: | |
| 8. Please choose your academic program: | MD |
| 9. What year are you in the program? | 2 |
| 10. Body of Abstract (300 words or less) | Rainbow Babies and Children’s Hospital broke ground this February on a new neonatal intensive care unit (NICU) scheduled to open in 2008. Plans for the new 40-bed NICU are centered around a single-family room design which provides a private environment with spaces for parents to sleep by their child’s bedside. This is a departure from the current NICU, which is organized in open wards holding up to six neonates in a shared area. The goal of this research project is to gather baseline data for a study of the effects of NICU design on stress experienced by parents of neonatal intensive care patients. The data collected in this preliminary study will be compared to data collected in a future investigation into stress experienced by parents of neonatal intensive care patients in the newly-designed NICU. We hypothesize that these studies together will provide evidence that the single-family room design of the new NICU will decrease the stress experienced by parents of neonatal intensive care patients. During a 6 month period, parents of NICU patients are approached at their child’s bedside to participate in this study, with a goal of enrolling 150 families. Anxiety levels of parents with children in the current NICU are measured using the State Trait Anxiety Inventory (STAI), a validated tool that assesses self-reported anxiety of adult subjects. A second, open-ended questionnaire asks subjects about their satisfaction, or discontent, with the current NICU environment. Data is pending as parent questionnaires continue to be distributed and returned until the end of the study period. Upon completion of the new NICU, a second phase of this study will proceed with a population of parents of patients in the new NICU, and the data collected from the two studies will be compared. |
| 11. What was your role in this project? | Development of protocol, distribution and collection of surveys (data collection) |
**Title**: Effect of cryopreservation on ovarian vessels' microvascular autografting

**Student Presenter**: Kathryn Feldman

**Co-workers and Collaborators**: Amr Kader, MD, Rakesh Sharma, PhD, Tommaso Falcone, MD, FRCSC, FACOG

**Advisor**: Tommaso Falcone, MD, FRCSC, FACOG

**Departments**: Obstetrics and Gynecology, Plastic Surgery

**Institutions**: Cleveland Clinic Foundation

**Support**: Crile Fellowship

**Academic Program**: MD

**Year in Program**: 2

**Body of Abstract (300 words or less)**

**Background**: Cryopreservation and autotransplantation of ovaries is an experimental strategy to preserve fertility. Present techniques result in severe ischemic damage of the autograft. Vascular grafting of cryopreserved whole ovaries was developed with the aim of improving post-transplantation ovarian ischemia. Our hypothesis is that cryopreservation may cause vascular endothelial damage increasing the risk of thrombosis, leading to post-transplantation vessel occlusion.

**Objective**: to study the effects of cryopreservation and thawing techniques on ovarian vessels’ structure, patency, and thrombus formation after microvascular anastomosis.

**Methods**: Three ewes underwent bilateral oophorectomy. The right ovarian vessels were immediately grafted to the deep inferior epigastric vessels on the ipsilateral side. The left ovarian vessels were cryopreserved for approximately 2 weeks and consequently thawed. After thawing, these vessels were grafted to the left deep inferior epigastric vessels. Two weeks later, all vascular grafts were explored and excised. Vessels were checked for structural changes, patency, and thrombus formation.

**Results**: Sheep #1 developed a seroma at the site of the fresh graft. The thawed vessels were so edematous that the grafting could not be performed. Sheep #2 had a functioning fresh graft, but did not recover from anesthesia. Sheep #3 had a successful fresh graft but only the cryothawed ovarian artery was grafted as the vein was varicosed and incompatible with the host vessel. On final exploration, the grafted fresh ovarian artery was functioning, and the vein was thrombosed. The grafted cryo-thawed artery was totally obliterated.

**Conclusion**: The preliminary observations on this technique showed severe limitations. First, the technique of cryopreservation used appears to cause edema of the vessels post thaw that makes microvascular anastomosis very difficult. The technique of cryopreservation needs to be refined.
altered to avoid this effect. Second, even if the microvascular anastomosis is technically possible the cryopreservation process seems to have caused endothelial damage resulting in graft occlusion. Third, the technical limitation of discrepancy between the vessels anastomosed may require a different anatomical site.

| 11. What was your role in this project? | Assisting in the bilateral sheep oophrectomies, helping to collect the vessels and capture images for data analysis, assisting in cryopreservation and thawing protocols. |
1. Title | Effects of Keratan Sulfate on Proteolytic Cleavage of the Aggrecan Core Protein

2. Student Presenter: | Chad M Fortun

3. Co-workers and Collaborators: |

4. Advisor: | Dr. Thomas Hering

5. Departments: | Department of Orthopaedics

6. Institutions: | Case Western Reserve University

7. Support: | AFAR

8. Please choose your academic program: | MD MS

9. What year are you in the program? | 2

10. Body of Abstract (300 words or less) | To date no data related to the initial hypothesis has been produced. Over the summer we performed a pilot study to determine the methods necessary to produce aggrecan substituted with KS and aggrecan deficient of KS.

We determined the most appropriate cell line to be a wild type MDCK cell line and a mutant MDCK cell which are substituted with KS and KS deficient respectively. We also determined it is necessary to utilize a nucleofector to nucleofect our MDCK cell lines in order to increase our efficiency in transiently transfecting them with the plasmid carrying the genes for aggrecan production.

This pilot study will allow us, in the coming months, to produce a large quantity of aggrecan substituted with KS and deficient in KS. This stock of aggrecan will allow us to carry out our original hypothesis.

“Hypothesis: We hypothesize that the substitution pattern of keratan sulfate on the aggrecan molecule, which may vary according to age, anatomical location or pathology, will modulate the proteolytic cleavage of aggrecan.”

Over the next few months and over the course of my research block the remaining questions will be addressed and answered.
| 11. What was your role in this project? | Principle investigator as part of a larger project by the lab's PI |
**Title**: Provider-level factors associated with HPV vaccine delivery to low-income residents in Cleveland.

**Student Presenter**: Marleny Franco

**Co-workers and Collaborators**: Stephen Asiimwe, MBChB, MS and Ann K. Avery, MD.

**Advisor**: Ajay K. Sethi, PhD, MHS.

**Departments**: Department of Epidemiology and Biostatistics at Case Western Reserve University, Department of Infectious Diseases at Metrohealth Center.

**Institutions**: Case Western Reserve University, University Hospitals of Cleveland, Metrohealth Center.

**Support**: T35 National Heart, Lung, & Blood Institute Research Opportunities for Minority Students Grant.

**Please choose your academic program**: MD

**What year are you in the program?**: 2

**Body of Abstract (300 words or less)**: Human papillomavirus (HPV), which causes cervical cancer, is thought to be the most common viral sexually transmitted infection (STI) in the United States. Cervical cancer is the third most common cancer in women in the U.S. In June 2006, the U.S. Food and Drug Administration approved Gardasil, a vaccine against strains 6 and 11 as well as 16 and 18, which cause approximately 90% of cases of genital warts and 70% of all cervical cancers, respectively. Although, prior to the vaccine’s release, studies showed physicians’ general approval and intention to recommend it, no studies have been published exploring these issues since the vaccine’s availability. Our goals were to assess healthcare providers’ attitudes, perceived barriers to vaccination and intention to recommend the vaccine to patients aged 9 to 26 years seeking low-cost or free health care in Cleveland and East Cleveland. Healthcare providers working in community health centers around the city were invited to complete a self-administered 68-item questionnaire. Due to delays in IRB approval, the data collection is currently still ongoing. Data collection and analysis is expected to be complete by December 2006. The results could potentially show significant discrepancies between providers’ reported intent to recommend the vaccine prior to its release compared to their intent and attitudes now that the vaccine is available. Additionally, results will reveal providers’ opinions regarding the age at which they feel it is appropriate to recommend the vaccine as well as the barriers they expect to encounter when recommending the vaccine to different age groups. This information would shed light on the attitudes that influence providers’ level of compliance with HPV vaccination guidelines and would be useful in designing appropriate interventions to enhance compliance.
<p>| <strong>11. What was your role in this project?</strong> | <strong>Co-investigator and data collector.</strong> |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>BMP4’s role in astrogliosis and scar formation following spinal cord injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Molly L. Fuller</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Rae Wang, Brian Rothstein, Anne DeChant</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Robert H. Miller</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Neurosciences</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NINDS</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>6</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Bone Morphogenetic Proteins (BMPs) are members of the Transforming Growth Factor-β superfamily of cytokines which have been shown to alter the proliferative, apoptotic, and differentiative states of neural stem cells. During embryonic development of the central nervous system (CNS), BMP4 promotes differentiation of neural precursors into astrocytes at the expense of oligodendrocytes. To investigate the continuing influence of BMP4 on the biology of astrocytes in the adult, we are using our established in vivo model of a demyelinating lesion of the rat spinal cord. By two days after the lesion, BMP4 levels were upregulated and glial fibrillary acidic protein (GFAP) expression was increased. Since increased GFAP expression is a sign of a “reactive astrocyte” and marks the astrogliotic scar that follows injury to the CNS, we looked for upregulation of other scar markers. By seven days post-lesion, chondroitin sulfate proteoglycan (CSPG), heparin sulfate proteoglycan, versican, neurocan, and phosphacan were all found to be upregulated at the lesion site. To simplify the analysis of cell types and cell signaling involved in this scar response, we prepared Type 1 astrocyte cultures from the CNS of postnatal day 2 rats. Type 1 astrocytes were shown to be responsive to BMP4 via an increase in the phosphorylation and activation of Smad1, the signaling molecule immediately downstream of the activated BMP receptor. In response to BMP4 treatment, GFAP and vimentin expression increased in treated cultures and CSPG expression was markedly upregulated. Our data show that BMP4 may play a critical role in the astrogliotic response of type 1 astrocytes to a CNS insult and formation of a scar. Understanding this response may allow for the development of interventions after CNS injury which would cause improved regeneration of CNS neurons and oligodendrocytes and recovery of nervous system functioning.</td>
</tr>
</tbody>
</table>
1. Title | The Role of BMP4 in Astrogliosis and Scar Formation following Spinal Cord Injury

2. Student Presenter: | Molly L. Fuller

3. Co-workers and Collaborators: | Rae Wang, Brian Rothstein, Anne DeChant

4. Advisor: | Robert H. Miller

5. Departments: | Department of Neurosciences

6. Institutions: | School of Medicine, Case Western Reserve University

7. Support: | This research is supported by grant #NS36674 to R.H.M.

8. Please choose your academic program: | MD PHD

9. What year are you in the program? | 7

10. Body of Abstract (300 words or less) | Bone Morphogenetic Proteins (BMPs) are members of the Transforming Growth Factor-β superfamily of cytokines which signal through intracellular molecules called Smads. BMP4 has been shown to promote differentiation of neural precursors into astrocytes at the expense of oligodendrocytes during development. We are investigating the role of continued expression of BMP4 in the adult central nervous system (CNS), and its influence on the biology of astrocytes in the injured spinal cord. In our rat model of a demyelinating lesion of the dorsal columns, injury leads to altered astrocyte behaviors, including cell hypertrophy, increased expression of glial fibrillary acidic protein (GFAP), and formation of a scar with accumulations of chondroitin sulfate proteoglycans (CSPGs). Local GFAP-positive astrocytes contain phosphorylated Smad1/5/8 in their nuclei, showing responsiveness to environmental BMP's. These activated astrocytes are present in the lesion before and during CSPG accumulation, which begins at 2 days post-injury. In vitro analysis of astrocyte responses show that treatment with BMP4 for 60 minutes induces a translocation of Smad1/5/8 from the cytoplasm to the nucleus and a dose-dependent increase in the phosphorylation of Smad 1/5/8. After 24 hours of BMP4 treatment, quantitative RT-PCR shows increased mRNA for several CSPG core proteins, including aggrecan, brevican, and neurocan. After 48 hours of BMP4 treatment, cells produce a dose-dependent increase in the amount of CSPG's deposited on the culture substrate. We hypothesize that a demyelinating lesion of the spinal cord causes a local increase in BMP4 signaling and dysregulation of CSPG expression by resident astrocytes. Inhibition of this response could limit scar formation and allow for improved recovery after CNS injury.
| **11. What was your role in this project?** | I am the primary researcher organizing and conducting the experiments under the supervision of my faculty mentor. |
GALLOGLY, MOLLY

1. Title
Role of Reversible S-glutathionylation in Regulating Cellular Survival: Focus on the Aging Heart

2. Student Presenter:
Molly Gallogly

3. Co-workers and Collaborators:
Edward Lesnefsky, David Starke, Sarah Stewart, Qun Chen

4. Advisor:
John Mieyal, PhD

5. Departments:
Pharmacology (Case) and Medicine (VA)

6. Institutions:
Case School of Medicine, Louis Stokes Cleveland Department of Veterans Affairs Medical Center

7. Support:
NIH T32 GM07250 (MMG), NIH P01 AG 15885 (JJM, EJL), NIH R01 AG 024413, VA Merit Review Grant (JJM)

8. Please choose your academic program:
MD PHD

9. What year are you in the program?
5

10. Body of Abstract (300 words or less)
Post-translational modification by reversible S-glutathionylation is an emerging redox signal transduction mechanism affecting diverse cellular processes, including hypertrophy, actin polymerization, growth signaling, calcium homeostasis, glucose metabolism, and transcription factor activation. Proteomic analysis of rat heart tissue reveals that global protein-SSG (P-SSG) levels, as well as individual P-SSG levels (e.g., GAPDH, actin) are increased following ischemia-reperfusion. We have discovered that content and activity of glutaredoxin (GRx), the major intracellular de-glutathionylating enzyme, is decreased in heart tissue from Fisher 344 rats, an established model of human aging. We hypothesize that in the aging heart, decreased GRx activity leads to increased P-SSG levels following an oxidative insult such as ischemia reperfusion. We expect such changes in glutathionylation status to influence signal transduction pathways that regulate contractility and cellular survival, contributing to the increased morbidity and mortality experienced by elderly patients who suffer from myocardial infarction. We have shown in a pilot study that ischemia-reperfusion leads to increased glutathionylation of actin and a ~100 kD membrane protein (coincident with SERCA2 immunoreactivity) in adult (6 month-old) Fisher 344 rats. We intend to compare these changes in glutathionylation status with those seen in elderly (24 m.o.) rats, and use cell culture models (primary adult and elderly cardiomyocytes and embryonic cells with knocked-down GRx) to study the effects of actin glutathionylation on cytoskeletal integrity, contractility and apoptotic signaling; and the effects of SERCA2 glutathionylation on calcium homeostasis.

1. Title
Kinetic Comparison of Human GRx1 and GRx2 as Deglutathionylation
Glutaredoxin (GRx) is a thiol-disulfide oxidoreductase (TDOR) that utilizes free glutathione (GSH) to reduce protein-glutathione mixed disulfides (P-SSGs), forming protein-SH and glutathione disulfide (GSSG). GRx-mediated de-glutathionylation of proteins such as actin, PTP1B, and Ras serves important roles in cellular redox balance and signal transduction (Shelton et al., 2005). Mammalian cells contain two GRx isoforms: GRx1, found in the cytosol and mitochondrial intermembrane space (Pai et al., 2006), and GRx2, localized to the nucleus and mitochondrial matrix (Lundberg et al., 2001). Although GRx2 displays <35% sequence identity to GRx1 (Gladyshev et al., 2001), it has an analogous active site motif (CXXC) and glutathionyl stabilization site (Bushweller et al. 1994, Yang et. al. 1998). Here we report that GRx2 also mimics GRx1 remarkably in its catalytic mechanism. Like GRx1, GRx2 displays ping-pong kinetics whereby the apparent KM and Vmax values for protein-SSG and GSH change in proportion to the concentration of the other substrate. We also determined the pKa of GRx2’s active site cysteine thiol by examining the pH dependence of enzyme inactivation by iodoacetamide. The active site cysteine’s pKa was determined to be 4.5, one pH unit higher than the corresponding pKa value for GRx1. If the catalytic principle of GRx2, like GRx1, is dependent on the pKa value of the enzyme-SH leaving group (Gilbert, 1990), Grx2 is predicted to display 25% of the activity of GRx1 for a common protein-SSG substrate. Indeed, with either BSA-SSG or cysteine-SSG, the catalytic efficiency of GRx2 is about 25% of that of GRx1. Finally, we demonstrate that while GRx2 can couple to thioredoxin reductase (TRase), as reported by Johansson et al. (2004), turnover of GRx2 by TRase is far less efficient than turnover by the preferred coupling enzyme, GSSG reductase (GRase), even when GRase and GSH are present at one-tenth of their typical intracellular concentrations. Thus, turnover by TRase is unlikely to serve as an important contributing mechanism to GRx2 activity in situ, even under low GSH ("oxidative stress") conditions.
1. Title
Kinetic Comparison of Glutaredoxin (GRx) Isoforms as Deglutathionylating and Glutathionylating Enzymes

2. Student Presenter:
Molly Gallogly

3. Co-workers and Collaborators:
David W. Starke, Amanda K. Leonberg

4. Advisor:
John J. Mieyal

5. Departments:
Pharmacology

6. Institutions:
Case Western Reserve University School of Medicine

7. Support:
NIH T32 GM008803, T32 GM07250, NRSA TRN 103171 (MMG); NIH R01 AG 024413 & P01 AG 15885, and VA Merit Review (JJM).

8. Please choose your academic program:
MD PHD

9. What year are you in the program?
7

10. Body of Abstract (300 words or less)
Glutaredoxin (GRx) is a thiol-disulfide oxidoreductase that utilizes glutathione (GSH) to reduce protein-glutathione mixed disulfides (protein-SSG). GRx-catalyzed protein deglutathionylation serves important roles in redox homeostasis and signal transduction, regulating diverse physiological and pathophysiological events including cytoskeletal organization, protein synthesis, calcium homeostasis, hypertrophy and apoptosis (Klatt & Lamas, 2000, Shelton et. al., 2005, Gallogly & Mieyal, 2007). Mammalian cells have two GRx isoforms: GRx1, localized to the cytosol and mitochondrial intermembrane space, and GRx2, localized primarily to the mitochondrial matrix (Pai et al., 2007). The kinetic behavior of GRx1 is well characterized (reviewed in Mieyal et al., 1995); however, little has been reported about the kinetics of GRx2. Here, we report that GRx2 exhibits key kinetic similarities to GRx1, including (1) selectivity for protein-SSG substrates, (2) a nucleophilic, double-displacement catalytic mechanism in which only the N-terminal active site Cys is required for catalysis, and (3) negligible substrate affinity, suggesting formation of an encounter complex that proceeds immediately to catalysis without reversible substrate binding. A key distinction between GRx1- and GRx2-mediated deglutathionylation is decreased catalytic efficiency of GRx2 (driven primarily by decreased Vmax for protein-SSG and GSH), which is partially explained by an increase in the pKa of GRx2’s active site cysteine, which serves as a
leaving group in the second, rate-determining step of the
deglutathionylation reaction. Prediction of GRx2’s likely contribution to
intracellular deglutathionylation activity is complicated by findings that the
enzyme exists primarily in inactive, FeS cluster dimers within the
mitochondrial matrix (Lillig et al., 2005). We propose that GRx2’s primary
intracellular role may be as a glutathionylating—rather than a
deglutathionylating—enzyme, based on reports that inactive GRx2 dimers
dissociate into active monomers upon exposure to reactive oxygen and
nitrogen species, and our observation that GRx2 can utilize oxidized
derivatives of GSH to promote glutathionylation of model protein
substrates.

| 11. What was your role in this project? | primary investigator |
Introduction: Current models propose that the principal function of Plexin is to bind and sequester active Rac1, removing it from the pool of GTPases that can interact with effector molecules, thereby reducing actin turnover and contributing to growth cone collapse. The Rac binding domain (RBD) contains a surface loop between an α and β helix. This loop has a CxxxC sequence which is similar to the CxxS motif indicative of a thiol-dependent redox enzyme. This suggests that under oxidative conditions, the RBD of Plexin can form disulfide bonds which may have effects on enzymatic activity and/or structural conformation. Oxidative signaling has already been implicated in a variety of other proteins and it has even been hypothesized that the protein MICAL exerts its effects by increasing Reactive Oxygenation Species (ROS) in the presence of Plexin.

Objective: To demonstrate that ROS can induce structural changes in the RBD at physiological levels and to elucidate these changes using SDS-Page, NMR, and CD techniques.

Results:
1. Both the Cys34 and Cys112 mutants formed dimers under previously demonstrated conditions, while the NoCys mutant remained in the monomeric form after exposure to Hydrogen Peroxide.
2. The incubation times showed no change in the ability of dimer to form.
3. Multiple exposures had no effect on the amount of dimer formed.
4. The molar concentration however did have an effect on the amount of dimer formed giving optimal conditions for either mutant (Cys112 50µM; Cys34 100µM) with an incubation time of 2hrs.
5. NMR data pending.
6. CD data pending.

Conclusions: Pending

| 11. What was your role in this project? | Research Assistant |
Dengue fever (DF) is a viral illness transmitted by the mosquito Aedes aegypti. It is the most important mosquito-borne disease affecting humans worldwide. Dengue is endemic in more than 100 tropical and sub-tropical countries, with 2.5 billion people at risk and an estimated 50 million new infections reported each year. Since a viable vaccine has yet to be developed, dengue prevention depends entirely on vector control. At present, little is known about subpopulation diversity in natural populations of A. aegypti, thus our goal was to develop novel microsatellite markers that might prove to be useful molecular tools in the study of genetic variability in A. aegypti populations. Microsatellites are some of the best neutral markers for population genetics studies, but in contrast to other mosquitoes, A. aegypti is known to be microsatellite-poor. Trimeric repeats were preferred since they produce less stuttering on gels. We searched GenBank entries directly for 16-21 mers with ≥40% GC content that flank perfect trinucleotide repeats and that would produce an amplicon of ~100-300 nucleotides. A single set of PCR conditions was used to eliminate many sources of error, to maximize efficiency and increase comparability across laboratories. In all we identified 4 promising microsatellites. These produced a simple pattern amplifying genomic DNA from laboratory-bred mosquitoes from Johns Hopkins University and the Oswaldo Cruz Foundation, Brazil. All markers produced either homo- or heterozygotes. They had heterozygosities of 72, 50, 25 and 88% and a maximum of 3 alleles using small samples of 8-10 individuals. The laboratory will continue to identify an additional 6 markers. These will be used to generate the genetic indices Fst and Ne so that the distribution of the vector and the effect of control programs could be more effectively monitored.
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. What was your role in this project?</td>
<td>research assistant</td>
</tr>
<tr>
<td>1. Title</td>
<td>Effects of Exercise and Nutrition Intervention on Depression and Eating Behavior Thoughts in Endometrial Cancer Survivors</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Karen Gibbins</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Vivian VonGruenigen, Heidi Gibbons, Steven E. Waggoner, Mary Beth Kavanagh, Jeffrey Janata, Kerry S. Courneya, and Edith Lerner</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Vivian VonGruenigen</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Gynecologic Oncology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>University Hospitals</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Background: Endometrial cancer survivors are typically plagued by comorbidities related to obesity. Diagnosis and treatment of cancer could serve as a teachable moment for patients to make lifestyle changes that would decrease these comorbidities. Long-term changes need to address not only behavior, but also emotional thinking and concerns. Question: In terms of depression and thoughts regarding eating behaviors, how are the cognitions of endometrial cancer survivors changed by a six month exercise and nutrition intervention? Methods: 45 patients post-treatment for early stage endometrial cancer were randomized to intervention or control groups for six month exercise and nutrition counseling. Patients completed the Beck Depression Index, 3 Factor Eating Inventory (EI), and Weight-Efficacy Lifestyle (WEL) questionnaires at baseline and post-intervention. Results: At baseline, 15% had mild depression, 4% had moderate depression, and 4% had severe depression. At 12 months, 16% had mild depression and 3% had moderate depression, with an overall decrease in Beck score of 2.5 (p &lt; 0.001). There was no difference in Beck score change between groups. EI revealed patient problems with eating restraint and did not show any difference between groups. WEL total scores were significant comparing baseline to 6 months (Difference = 29, p &lt; 0.05) and baseline to 12 months (Difference = 3.5, p &lt; 0.05). The significant factor subsets in the intervention group were Social Pressure and Positive Factors. Conclusion: The six month intervention was effective in positively changing mental state regarding efficacy in Social Pressure and Positive Factors. These cognition changes suggest feasibility of maintaining the weight and exercise changes made during intervention.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Data collection assistance, analysis, write-up (with help on data collection from Heidi Frasure)</td>
</tr>
</tbody>
</table>
**Maximizing Production of Dissociated Purkinje Neurons for use in Patch Clamp Analysis**

**Tyler Gifford**

Ovsepyan, S. and Friel, D.

Friel, D.

Neuroscience

Case Western Reserve University School of Medicine


Womack and Khodakhah, Dendritic Control of Spontaneous Bursting in Cerebellar Purkinje Cells. Journal of Neuroscience, 2004 • 24 (14) 3511–3521

**MD**

2

Background and rationale: P/Q type Calcium channels are expressed on the surface of Purkinje cells in mouse cerebellum. Therefore the Purkinje cells are a good candidate for studying calcium current and its effect in P/Q type mutants. My work focused on developing a reproducible technique for preparing dissociated Purkinje cells and measuring current and voltage using patch clamping.

Question or hypothesis that I addressed: What is the optimal preparation method for preparing dissociated Purkinje cells for patch clamping?

Methods used to pursue this question: Previously established procedures for preparation of Purkinje neurons have been published by Raman and Bean (1999) and Womack and Khodakhah (2004). Based on these techniques, a procedure was developed for dissociating Purkinje neurons that maximally preserved dendritic arborization without compromising cell viability. Variables included exposure time to protease and repetitions of trituration. Outcome measures included number of live cells obtained per brain slice and preservation of dendritic tree. Cell viability was confirmed with detection of normal electrical activity detected with patch clamp.

Results: Maximum live cells were obtained with a protease exposure time of 12 minutes. Five repetitions of rapid trituration produced adequately dissociated cells with detectable dendritic trees. Patch clamping under voltage clamp detected normal oscillations and spontaneous firing in
dissociated cells.
Conclusion: A customized technique based on methods published by Raman and Bean and materials published by Womack and Khodakhah produced the maximum number of viable cells with detectable dendritic trees and normal electrical activity.

| 11. What was your role in this project? | Investigator |
HIV infection is characterized by an increased proportion of circulating T-lymphocytes found in S-phase of the cell cycle. Previous studies suggest S-phase T-cells are more likely to undergo apoptosis instead of completing the cell cycle, and proportions of these cells are directly related to plasma HIV levels. We use uptake of bromodeoxyuridine (BrdU), a thymidine analogue that is incorporated into newly synthesized DNA, to identify cells in S-phase. These cells are detected by flow cytometric analysis using a fluorochrome labeled antibody to BrdU. Frozen peripheral blood mononuclear cell (PBMC) samples from HIV+ patients who have been followed in our clinic are available for research, but studies suggest frozen samples are not efficiently labeled with BrdU. These samples could provide a resource for testing the relationship between rates of CD4 cell loss and frequencies of circulating S-phase T-cells over time. The purpose of this study was to identify cellular markers that permit detection of lymphocytes in S-phase of the cell cycle when examining frozen samples.

We reasoned that identifying T-cells expressing Ki-67, an intracellular protein present during G1, S, and G2/M phases of the cell cycle, and cyclin A, another intracellular protein characteristic of S-phase cells, might provide an alternative method for detecting cells in S-phase. We tested this approach by stimulating healthy PBMCs with anti-CD3 antibodies to induce cell cycle progression in vitro. T-cells were analyzed for co-expression of Ki-67, cyclin A, and BrdU. Analyses of CD4+ lymphocytes demonstrated that stimulated cells labeled with BrdU corresponded to cells expressing both Ki-67 and cyclin A. Cells from these samples were frozen and thawed after 1 week to test for the stability of cyclin A in freeze-thaw conditions. Expression of this marker was not altered by the freeze-thaw method, suggesting it should be stable in
<table>
<thead>
<tr>
<th><strong>11. What was your role in this project?</strong></th>
<th><strong>Student Investigator</strong></th>
</tr>
</thead>
</table>

cryopreserved PBMC samples.
Methoxyamine and benzylguanine potentiate the therapeutic efficacy of temozolomide in a human glioma cell line

Daniel Glazer

Alina Bulgar, John Donze, Yanling Mao

Lili Liu and Stan Gerson

Hematology/Oncology

Case Western Reserve University

American Cancer Society and the NIH

MD

2

This project focused on the combined cytotoxic effects of temozolomide, methoxyamine and benzylguanine on a human glioma cell line. The purpose of my work was to determine if the effect of these three drugs in combination is greater than the effect of temozolomide alone. This is an important question because malignant cells are able to repair the DNA damage caused by temozolomide using base excision repair (BER) and the protein MGMT. These two repair pathways can be blocked by the inhibitors methoxyamine and benzylguanine, potentiating temozolomide cytotoxicity. To determine the efficacy of the drugs in combination I constructed a survival curve relating the drug dose to percent survival of glioma cells. Next, I did an AP site analysis to measure the percent of abasic sites that are bound by methoxyamine and thus blocked from repair. To quantify the effect of these drugs in cell culture I used Annexin V staining and cell cycle analysis to determine the amount of apoptosis and cell cycle arrest respectively. Lastly, I used JC-1 staining to examine the level of mitochondrial damage caused by these compounds. These experiments clearly show that methoxyamine and benzylguanine potentiate the cytotoxic effects of temozolomide. In combination they are roughly ten times more potent than temozolomide alone as shown by the survival curves. AP site analysis demonstrated a 50% blocking of abasic sites by methoxyamine, leading to a greater accumulation of DNA damage than would be expected with temozolomide alone. The results from Annexin V, cell cycle analysis, and JC-1 staining were consistent with these findings, as the three drug combination proved to be superior to temozolomide alone.

It is clear that benzylguanine and methoxyamine have a synergistic effect when used in combination with temozolomide. By inhibiting the BER and MGMT repair pathways, temozolomide becomes a much more effective
| 11. What was your role in this project? | I carried out all the experiments and analyzed the data |
Title: Role of Cytosolic Phospholipase A2 in the Increased Lung Inflammation of a Patient with Cystic Fibrosis

Student Presenter: Gustavo Gomez

Co-workers and Collaborators:

Advisor: Aura Perez

Departments: Cystic Fibrosis

Institutions: Case Western Reserve University

Support: Crile Fellowship

Academic Program: MD MS

Year in Program: 2

Body of Abstract (300 words or less):

This experiment attempted to obtain information about the difference in the pathophysiology of inflammation between airway epithelial cells of a normal individual and those from a person with Cystic Fibrosis (CF). Lung inflammation is, among other factors, linked to the metabolism of arachidonic acid (AA) which is known to be present at increased concentrations within the airway epithelial cells of CF patients. Upon activation by calcium, cytosolic phospholipase A2 (cPLA2) translocates to intracellular membranes to initiate the synthesis of AA. This experiment focused on tracking the translocation of cPLA2 to determine its potential role in the augmented level of respiratory inflammation associated with CF.

16 HBE cells are grown on a filter allowing for the expression of apical and basal surfaces as they would in vivo. These are transfected with a plasmid (pEGFP(C3)-cPLA2?) resulting in the expression of cPLA2 bound to a GFP molecule which fluoresces under 527nm emission. Additionally, cells are exposed to DAPI 33258 (20?g/ml) to facilitate visualization of the nuclei. Much of this experiment involved the optimization of: concentration of DAPI and transfection reagents, location to apply the reagents (basolateral, apical or both sides), cell confluency at transfection, and interval of time between transfection and viewing. Ionomycin(10?M) is applied to transfected cells to activate cPLA2 and the translocation is viewed and recorded using a Leica DM 6000 Upright Microscope and Metamorph 4.6.

Work continues in optimizing the experimental conditions. Anomalies involving changes in pH and nuclei size upon addition of ionomycin require further investigation. A better system of application of ionomycin must
also be devised. Finally, the use of a CFTR inhibitor, allowing the mimicry of a CF cell, has yet to be explored under these conditions. Once the proper methods have been formulated, a subsequent experiment may finally answer the initial hypothesis.

| 11. What was your role in this project? | Lab Researcher |
| 1. Title | Hypoxia-inducible factor-1-alpha expression increases after photodynamic therapy using the silicon phthalocyanine Pc 4 |
| 2. Student Presenter: | David J. Grindler |
| 3. Co-workers and Collaborators: | Andrew H. Hsia, Diana Santo Domingo, M.D., Janine D. Miller, M.D., Kevin D. Cooper, M.D., Elma D. Baron, M.D. |
| 4. Advisor: | Elma D. Baron |
| 5. Departments: | Department of Dermatology |
| 6. Institutions: | Case Western Reserve University / University Hospitals Case Medical Center |
| 7. Support: | |
| 8. Please choose your academic program: | MD |
| 9. What year are you in the program? | 2 |
| 10. Body of Abstract (300 words or less) | In this study we looked at the possibility of using hypoxia inducible-1-alpha (HIF-1a) as a marker for clinical response after photodynamic therapy (PDT) with the silicon phthalocyanine Pc 4 of cutaneous T-cell lymphomas. In dermatology, PDT is currently being applied as a treatment for several hyperproliferative diseases such as actinic keratoses and various cutaneous malignancies. Silicon phthalocyanine Pc 4 is a second generation photosensitizer that more efficiently absorbs tissue-penetrating red light than previously-used photosensitizers. The photodynamic mechanism utilizes oxygen to generate singlet oxygen, which then acts on cellular substrates- a process that potentially creates hypoxia in the tissue and also leads to apoptosis. These events can be monitored using HIF-1a as a hypoxic marker and caspase-3 as an indicator of early apoptosis. The purpose of this study was to examine changes in these two markers in patients-post PDT. Punch biopsies of skin lesions and control/untreated tissues were obtained 24 hours after treatment, and sections from these samples were immunostained using antibodies against HIF-1a and caspase-3. The percentage area of positive staining in the epidermis for both markers was determined using Image-Pro interactive image analysis software on ~10 measures per sample. We observed significant increases in caspase-3 in the epidermis of post PDT biopsies, with 25.01% noted among treated patients versus untreated control samples from the same patient, which only showed a 15.5% increase (p<0.005). Interestingly, significant increases were also found for HIF-1a, such that 29.7% of the epidermis in treated lesions showed positive staining versus 11.3% in untreated controls (p<0.005). These findings indicate that Pc 4-PDT treatment leads to significant increases in caspase-3, and that HIF1-a expression increases after Pc 4-PDT. |
# Exhaled nitric oxide and asthma- what can FENO really tell us?

**Student Presenter:** Natalia M. Grob

**Co-workers and Collaborators:**

**Advisor:** Raed A. Dweik

**Departments:**
1: Case Western Reserve University, School of Medicine, Cleveland, OH
2: Lerner Research Institute and Cleveland Clinic, Cleveland, OH

**Institutions:**
2: Department of Pulmonary, Allergy, and Critical Care Medicine and Pathobiology

**Support:**
2. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med 2005; 171:912-930

**Please choose your academic program:** MD

**What year are you in the program?** 2

## Body of Abstract (300 words or less)

Background: Exhaled NO (FENO) measurements have been utilized as a marker to diagnose asthma as well as a non-invasive tool for monitoring airway inflammation and the response to anti-inflammatory medications. One area where this non-invasive monitoring may be helpful is for asthmatic athletes as they train for competitive events. The effect of exercise training on airway inflammation in asthma is not clear. Furthermore, FENO values vary among different groups and no clear reference values exist for determining what a FENO value suggests about a patient.

Hypothesis: We hypothesized that in the course of training an asthmatic individual may experience worsening of lung inflammation reflected in FENO levels that may be too subtle to detect by conventional methods like spirometry. The recent availability of a portable NO analyzer (NIOX-MINO) system allowed us to test this hypothesis.

Methods: Data was collected from an asthmatic patient training for a half-marathon on both the desktop and the portable NO analyzers daily for 8 weeks.

Results: Average NO levels measured in the standard system correlated well with the two portable MINO analyzers ($r^2 = 0.7869, r^2 = 0.8786$; $p < 0.0001$); additionally, there was a strong correlation between the two MINO devices ($r^2 = 0.8831; p < 0.0001$). As the number of miles run increased, average NO levels decreased; a strong negative correlation...
was found between the number of miles run and NO, regardless of the device used [NIOX $r^2 = -0.6$; MINOA $r^2 = -0.5$; MINOB $r^2 = -0.4$; All $p < 0.05$). FEV1 and PEF, however, did not change significantly as the miles run increased ($p = 0.4$) and 0.2 respectively. In order to put these NO levels in context, we reviewed the published literature for FENO levels asthmatic and healthy control groups. While there is considerable variation among published NO values that has lead to some confusion, some patterns emerged from or review. The geometric mean for FENO ranged from 11 ppb to 23 ppb in healthy control populations. For asthma, FENO geometric mean ranged from 25 ppb to 52 ppb. FENO greater than 47 ppb was suggested as a good predictor of steroid responsiveness and a value less than 35 ppb was suggested as a marker of good asthma control.

Conclusions: A new portable NO analyzer is reliable and can be used for non-invasive monitoring of airway inflammation in asthma. Exercise training in asthmatics was associated with a decrease (improvement) in NO levels but no significant change in FEV1 and PEF. This suggests that exhaled NO levels maybe more sensitive to changes in the airway as a result of exercise than traditional pulmonary function testing. Although considerable variation exists among NO values described for normal healthy and asthmatic populations reviewed, the recent inclusion of FENO measurement in the National Health and Nutrition Examination Survey NHANES is expected to provide more useful population-based normative values.

Keywords: asthma, exhaled nitric oxide, reference value, airway inflammation, exercise
There is an 11-fold and 16-fold increase in cancer incidence and mortality comparing patients younger and older than age 65, respectively (1). According to the U.S. Census Bureau statistics, the U.S. population will double in citizens aged 65 or older, from 34 million in the year 2000 to 70 million in 2030.

Currently, oncologists use three strategies when treating an older patient: 1. history and physical (age), 2. Karnoksky Performance Status (range 0-100), and 3. ECOG (Eastern Cooperativity Oncology Group) Performance Status (0-5). These measures do not sufficiently assess an older patient’s functional age. One goal of geriatric oncologists is to create a measure that will aid oncologists in determining whether a patient needs an altered chemotherapy plan because of increased risk for toxicity. In my summer research, the utility of a geriatric assessment is tested. Six aspects of each patient are addressed in the questionnaire: functional status, cognition, comorbidities, nutrition, polypharmacy, and psychosocial. Patients are selected based on five criteria: age 65 or older, beginning chemotherapy for adjuvant treatment or metastatic disease, pathologic confirmation of cancer, understands English, and able to provide informed consent. The primary objective of this project is to determine whether the geriatric assessment predicts toxicity from the chemotherapy regimen. The secondary objective is to assess for longitudinal impact of cancer and chemotherapy on a patient’s functional assessment. As a two-year project, with multi-center involvement, data is still being collected.

A second project involved analyzing over 200 mailed geriatric assessment questionnaires completed at MSKCC and City of Hope. The goal was to assess for links between functional status, using patient’s responses to instrumental activities of daily living (IADLs)/activities of daily living (ADLs), and their comorbidities, to test whether specific comorbid conditions relate...
Currently, data is being analyzed by the department of biostatistics.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. What was your role in this project?</td>
<td>Clinical Research Assistant</td>
</tr>
</tbody>
</table>
Title: Outcomes of Patients Declined for Cardiac Allograft Transplantation

Student Presenter: Ihab Halaweish

Co-workers and Collaborators: Randall Starling, David Taylor, Jim Campbell, Deanna Hartman, Kristin Ludrotsky

Advisor: Dr. Gonzalo Gonzalez-Stawinski

Departments: Department of Thoracic and Cardiovascular Surgery

Institutions: Cleveland Clinic

Support: MD

What year are you in the program? 2

Body of Abstract (300 words or less)

Objective:
To determine the short- and long-term outcomes of patients declined for heart transplantation.

Background
A major problem in heart transplantation is the increasing numbers of heart failure patients considered transplant candidates and the limited number of donor organs available; thus, appropriate patient selection requires a vigorous evaluation process. There is little knowledge regarding the outcome of patients referred for heart transplantation evaluation and denied due to existing contraindications.

Methods
We performed a retrospective review of 210 patients evaluated and denied after evaluation for heart transplantation at our institution between January 2000 and May 2007.

Results
The mean age was 53.7 years (17-77 years) with a male to female ratio of 4.1:1. The most common etiology of heart failure included ischemic cardiomyopathy in 120 (57%) and dilated cardiomyopathy in 71 (34%). 145 (69%) patients were in NYHA class III, 40 (19%) were in NYHA class II, and 25 (12%) were in NYHA class IV. Common reasons for declining included psycho-social reasons in 52% and being judged too well in 21%. Most patients were denied because of multiple reasons however. For example, 54 (25.7%) patients were denied for two reasons, 27 (12.9%) for three reasons, and 25 (11.9%) were denied for four or more reasons. Overall patient survival at a mean follow-up of 2.4 years was 41%. Mean survival
for patients deemed too well was 67% compared to 39% and 20% for NYHA class III and IV patients respectively. Survival for patients discharged with inotrope therapy was merely 29%. Post declination, 28 patients (13%) were listed elsewhere and 14 (6.7%) were ultimately transplanted at other centers.

Conclusion:
In this single center study, most patients who are deemed to well for transplantation survive with medical management; however, a significant proportion of patients go on to being listed and/or transplanted at outside facilities.

Background
Heart transplantation has become standard therapy for end-stage heart failure and is widely recognized as a modality for prolonging life and improving its quality in carefully selected patients. A major problem is the increasing numbers of heart failure patients considered transplant candidates and the limited number of donor organs available; thus, appropriate patient selection requires a vigorous evaluation process. There is little knowledge regarding the outcome of patients referred for heart transplantation evaluation and denied due to existing contraindications.

Methods
We performed a retrospective review of 210 patients evaluated and denied after evaluation for heart transplantation at our institution between January 2000 and May 2007. Variables collected for analysis included demographics, reasons for decline, and short- and long-term outcomes.

Results
The mean age was 53.7 years (17-77 years) with a male to female ratio of 4.1:1. The most common etiology of heart failure included ischemic cardiomyopathy in 120 (57%) and dilated cardiomyopathy in 71 (34%). 145 (69%) patients were in NYHA class III, 40 (19%) were in NYHA class II, and 25 (12%) were in NYHA class IV. Common reasons for declining included 52 % declines due to psycho-social reasons, and 21 % because of being judged too well for listing. However, most patients were denied because of multiple reasons. For instance, 54 (25.7%) patients were denied for two reasons, 27 (12.9%) for three reasons, and 25 (11.9%) were denied for four or more reasons. Overall patient survival at a mean follow-up of 2.4 years was 41%. Mean survival for patients deemed too well was 67% compared to 39% and 20% for NYHA class III and IV patients respectively. Survival for patients discharged with inotrope therapy was merely 29%. Post declination, 28 patients (13%) were listed elsewhere and 14 (6.7%) were ultimately transplanted at other centers.

Conclusion:
In this single center study, most patients who are deemed to well for transplantation survive with medical management; however, a significant proportion of patients go on to being listed and then transplanted at outside facilities.
| 11. What was your role in this project? | Investigator |
HAMPOLE, ASHWIN

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Comparison of Myocardial Perfusion Using Tc-99m Sestamibi SPECT and Rubidium-82 PET: Contemporaneous Same-day Procedures With a Single Pharmacologic Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Ashwin V. Hampole</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Jeff Kolthammer, Patrick Wojtylak, Michaela Devlin, Peter Faulhaber, Robert Jones, Lina Mehta, and James O'Donnell</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Zhenghong Lee</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Radiology, Division of Nuclear Medicine</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University and University Hospitals</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Industrial grant from Philips Medical Systems Inc., &quot;Nouveau Heart&quot;</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>The assessment of myocardial perfusion (MP) has become an important aspect of the diagnostic and prognostic work-up of patients with coronary artery disease and left ventricular dysfunction. Patients with ischemic myocardium have been shown to benefit from revascularization with an improvement in LV function and a favorable prognosis. Several comparisons of myocardial perfusion Tc-99m SPECT and Rb-82 PET have been conducted and reported in the literature. However, a comparison between the two modalities acquired under identical conditions has not been performed. The purpose of the project was to assess the accuracy of SPECT and PET myocardial perfusion imaging (MPI) studies when both are done sequentially on the same day, after the same patient preparation, and from a single episode of pharmacologic stress with intravenous vasodilators. We hypothesized that PET imaging could offer a better alternative for myocardial perfusion imaging as compared to SPECT. By consensus and without clinical information, 4 experienced nuclear radiologists have interpreted image data from patients recruited from those referred by University Hospitals cardiologists for routine clinical MP SPECT/Tc-99m imaging who are likely to undergo subsequent coronary angiography or have recently undergone such angiography within the preceding 90 days. SPECT scans were acquired on a Cardio-60 system and PET scans on an ECAL ACCEL scanner. ROC curves are being used to determine if PET MPI is superior to SPECT MPI in terms of diagnostic accuracy, using echocardiography, conventional coronary angiography or CT-based angiography as the gold standard measurement. Results are currently being analyzed.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>I was responsible for scheduling training sessions with the physician observers, analyzing the training data, coordinating reading sessions, archiving the data, and analyzing the data.</td>
</tr>
<tr>
<td>1. Title</td>
<td>Asthma: Severity Assessment and Treatment in the Emergency Room</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Rachel Hampton</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Peter Knoll</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Cydulka</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>MetroHealth Emergency Department</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>MetroHealth and Case Western University School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>None</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Background: The recently published Guidelines for the Diagnosis and Treatment of Asthma from the NIH National Asthma Education and Prevention Program place considerable emphasis evaluation of asthma control. Study objective: The purpose of this study is to compare patient perception of asthma control with asthma control assessed by objective measures among emergency department (ED) patients. A secondary objective of this study is to compare patient perception of asthma control with physician perception of control in this population. Methods: Study population: asthmatics between 18 and 54 years old presenting to the MetroHealth ED with previously diagnosed asthma. Structured interviews regarding medications, asthma and other medical history were conducted. Patients were asked to assess their asthma control and complete the Juniper “Mini Quality of life Questionnaire” [MQLQ] and QualityMetric “Asthma Control Test” [ACT]. Treating physicians were then asked to assess the patient’s level of asthma control. Results: 116 patients were interviewed. 21% of patients assessed to have inadequate asthma control by the ACT assessed their asthma to be “well controlled” or “completely controlled.” 16% of patients assessed to have inadequate asthma control by the ACT were assessed by physicians to be “well controlled,” while 36% of these patients’ asthma control was not even addressed by physicians. Correlation between patient and physician assessment of asthma control was poor (r=0.27). 38% of patients who judged their asthma control to be “not controlled” or “poorly controlled” were judged to be “well controlled” or “completely controlled” by the treating physician, while 12% of patients who judged their asthma control to be “well controlled” or “completely controlled” were judged to be “not controlled” or “poorly controlled” by the treating physician. Conclusions: Agreement is poor between subjective assessment of asthma control and assessment of asthma control using objective measures. Agreement between patient</td>
</tr>
</tbody>
</table>
assessment and physician assessment of asthma control is also poor. We recommend using objective measures to assess asthma control among emergency department patients.

<p>| 11. What was your role in this project? | Interview Patients |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>A comparison of femoral neck version measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Daniel E. Hart</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Paul Toogood</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Daniel Cooperman, M.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Orthopedics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University School of Medicine, University Hospitals of Cleveland, and the Cleveland Museum of Natural History</td>
</tr>
<tr>
<td>7. Support:</td>
<td>None</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Femoral Neck Version is intrinsic to the stability of the hip. Version relates the angle of the head and neck of the femur to the frontal plane of the body. Unlike the clinical setting, version measurements may be taken independently of the position of the femoral shaft in a lab setting. The purpose of this study was to determine the significance of the variation between true femoral neck version measurement and version measurement typically taken in a clinical scenario.

Using the femur archives at the Hamman Todd Collection in Cleveland, OH the variation in version measurements was compared in differently positioned femurs. The specimens came from two categories of version as measured previously in the classic prospective view, with the plane of the femoral neck parallel to the plane of measurement (see below). Anteverted femurs were classified as having version measurements greater than 20 degrees. Normal femurs had angles between 0 and 5 degrees.

Femurs in each of three version categories were measured in two different positions, estimating the anatomic position as well as the clinical orientation. The anteverved group of 15 femurs and the normal group of 10 femurs were combined to produce a sample of 25 femurs. The measurements in the prospective and anatomical positions of all 25 femurs were compared using a two tailed t test. The groups were assumed to have equal variances. There was a statistically significant difference between the version measurements of femurs in the prospective position as compared to those same femurs measured in the anatomic position (P = .031). The conventional measurement of femoral neck version may not be representative of the actual version in some cases. Measurement on CT scan may only be accurate for a particular range of neck/shaft angles. |
| 11. What was your role in this project? | Designed and implemented the project, took photographs, and wrote the abstract. |
## IL-17 Induces Chemokine Expression via mRNA Stabilization

### 1. Title
IL-17 Induces Chemokine Expression via mRNA Stabilization

### 2. Student Presenter:
Justin Hartupee

### 3. Co-workers and Collaborators:

### 4. Advisor:
Thomas Hamilton

### 5. Departments:
Department of Immunology

### 6. Institutions:
Lerner Research Institute, Cleveland Clinic

### 7. Support:

### 8. Please choose your academic program:
MD PHD

### 9. What year are you in the program?
4

### 10. Body of Abstract (300 words or less)
IL-17 is a T cell derived cytokine that plays an important role in both host defense and autoimmunity by driving pro-inflammatory gene expression. However, the molecular mechanisms by which this induction occurs are not well understood. We have used the mouse chemokine CXCL1 (KC) as a model to study this process. KC expression is known to involve both the initiation of transcription as well as stabilization of the rapidly decaying mRNA. KC followed the typical pattern of IL-17 regulation in that IL-17 alone stimulated little expression, but it could cooperate with TNFa to induce a synergistic response. We have determined that IL-17 is a relatively poor stimulus for KC transcription and the activation of the transcription factor NF-kB. However, both actinomycin D chase experiments and studies using a tetracycline-regulated reporter indicate that IL-17 prolongs the half-life of the KC mRNA. Thus TNFa and IL-17 cooperate because they each provide half the requirements for full gene expression. TNFa induces transcription while IL-17 drives mRNA stabilization. IL-17 induced stabilization required the cytoplasmic adaptor Act1, which has recently been reported to interact with the IL-17R and to be required for the induction of gene expression. TRAF6 is recognized to function downstream of Act1 to mediate IL-17 induced NF-kB activation. TRAF6 also plays a role in signaling in response to other stimuli that result in KC mRNA stabilization such as IL-1 and toll like receptor ligands. This association suggested that TRAF6 may be part of a common signaling cascade that drives mRNA stabilization in response to multiple stimuli. However, using both a dominant negative construct and deficient cells we have determined that mRNA stabilization in response to IL-1 and IL-17 does not require TRAF6. This data indicates the existence of an uncharacterized TRAF6 independent signaling pathway that mediates mRNA stabilization.
| 11. What was your role in this project? | Worked with mentor to design experiments. Performed all experiments. |
## A Quantitative Description of Prostatic Chronic Inflammation and Its Transition to Prostate Cancer

**Student Presenter:**
DJ Harvey

**Co-workers and Collaborators:**

**Advisor:**
Dr. Sanjay Gupta & Dr. Sanjeev Shukla

**Departments:**
Urology

**Institutions:**
University Hospitals of Cleveland Case Medical Center/ Case Western Reserve University School of Medicine

**Support:**
Crile Grant

**Please choose your academic program:**
MD

**What year are you in the program?**
2

### Body of Abstract (300 words or less)
Increasing evidence suggests that proliferative inflammatory atrophy (PIA) of the prostate is a possible neoplastic precursor for prostate cancer (PCa). Previous studies focused on radical prostatectomies of PCa positive patients. We examined prostate biopsies of PIA positive - PCa negative patients that subsequently developed PCa within 5 years following the PIA positive biopsies. We examined paraffin-embedded prostate biopsies (n=18) using quantitative immunohistochemistry for the presence of the inflammatory markers Cox-2 and iNOS, the cell survival marker Bcl-2, the genome protection marker GST, the prostate basal cell marker p63, and the prostate neoplasticity maker AMACR. The results of our data are still being collected however; early interpretation suggests that PIA positive biopsies are a positive indicator of neoplastic development.

**What was your role in this project?**
Primary Research Assistant
**1. Title**
The Search for Metastatic Colon Cancer Gene Translocations

**2. Student Presenter:**
Le (Lucy) He

**3. Co-workers and Collaborators:**
Dr. Lois Myeroff

**4. Advisor:**
Dr. Sanford Markowitz

**5. Departments:**
Department of Medicine, Ireland Cancer Center, University Hospitals of Cleveland

**6. Institutions:**
Case Western Reserve University and Howard Hughes Medical Institute

**8. Please choose your academic program:**
MD

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**
Colon and rectal cancers are a major public health concern constituting over 1 million cases of new cancers and 500,000 deaths worldwide in 2002. Chromosomal rearrangements have long been recognized in cancers of the lymph and blood, but have not been well characterized in solid tumor carcinomas. Recently, a prostate cancer gene translocation was found using a bioinformatics approach. Based on this methodology, bioinformatics data mining from the latest exon microarrays was undertaken to determine if such a gene translocation might exist in metastatic colon cancers. Assuming a gene involved in a translocation exhibits differential expression between it's 5' and 3' ends, a comparison of differential exon expression between the 5'-most and 3'-most exons of a gene was performed to find candidate translocation genes. Exon microarray data was available for Normal Colon, Stage B Colon Cancers, and Metastatic Colon Cancers. A novel algorithm was utilized to compare the relative 5' and 3' exon expression levels normalized by overall gene expression and this generated the Exon Expression Index (EEI). Significantly different EEI's between Normal and Metastatic samples found four candidate translocation genes (YY1, AMMECR1, FUCA1, ABHD3, and PEX26/TUBA8); two candidate genes were found comparing Stage B to Metastatic samples (GPR126 and PLAU). Further analysis also revealed five genes turned on in Metastatic, but turned off in Normal samples (CDH3, JUB, TRIB3, CCSP1, ETV4). CCSP1 has previously been validated as a gene turned on in colon cancer, but off in normal colon. Currently, wet lab validation of the in silico findings are underway to determine which of the gene candidates may be part of a gene translocation unique to metastatic colon cancer. Further bench validation of genes turned on in metastatic colon cancer, but turned off in normal colon may also yield further information about the pathogenesis of colon...
| 11. What was your role in this project? | All bioinformatics and data mining analysis work to find candidate genes of interest. |
**HEAPHY, JOHN**

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Phthalocyanine 4 (Pc 4)-Photodynamic Therapy for the Treatment of Benign Viral Induced Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>John Heaphy</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Richard Lee M.D.</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Kumar Alagramam Ph.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Otolaryngology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>CWRU</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>

| 10. Body of Abstract (300 words or less) | Recurrent Respiratory Papillomatosis (RRP) lacks a satisfactory treatment modality. Photodynamic therapy (PDT) is the use of light to activate an exogenous photosensitizer to initiate physical and chemical changes within a targeted cell population for therapeutic effect. Pc4, a photosensitizer, is a silicon phthalocyanine ring that works by targeting mitochondrial membranes and activating cellular pathways of apoptosis through generation of reactive oxygen species. To test the efficacy of Pc 4 PDT for the treatment of virally induced papillomas, a xenograft model where New Zeland white rabbit epithelium was grafted on to the backs of SCID mice was used. The rabbit epithelium was harvested from the backs of the rabbit’s ears. Xenografts 7 mm in diameter were punched out and transplanted to the backs of SCID mice, two grafts per mouse. After the grafts healed, a subset of the xenografts were infected with Cottontail rabbit papilloma virus (CRPV). Once the papillomas formed the mice received tail vein injections of Pc 4. After 48 hours, to allow for washout of Pc 4 from tissues that do not have rapidly dividing cells, the skin grafts were exposed to laser light from a tunable Argon pumped-dye laser at a wavelength of 675 nanometers to activate the photosensitizer. Results and conclusion: Of the 11 mice that were treated with Pc4 PDT to remove CRPV induced papillomas, 10 were successful in complete removal of the growth. Of those 10 which were successfully treated, 8 have subsequently remained tumor free several weeks after treatment. These mice are still being monitored for potential papilloma regrowth. Data from the current study suggests that Pc 4-PDT is effective in eradicating virally induced papillomas in the xenograft model. However, long term studies are necessary to validate the efficacy of Pc 4-PDT against virally induced papillomas and their recurrence. |
| 11. What was your role in this project? | I was the only one working on it |
### 1. Title
The Role of Th17 Cells in Autoimmunity

### 2. Student Presenter:
Marc Heikens

### 3. Co-workers and Collaborators:
Cong-Qiu Chu, M.D., Ph.D.

### 4. Advisor:
Keith Elkon, M.D.

### 5. Departments:
Immunology

### 6. Institutions:
University of Washington

### 7. Support:
Arthritis Foundation Pacific Northwest Chapter
Crile Research Fellowship

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)
The inflammatory mechanisms of rheumatoid arthritis (RA) have yet to be fully elucidated. Cytokines produced by monocytes/macrophages proven to be involved include TNF-α, IL-1, and IL-6. More recently, a T cell cytokine, IL-17 has been found to play an important role in mouse models of arthritis. High levels of IL-17 have been found in RA joints and a new subset of T helper cells called Th17 cells have been implicated in the pathogenesis of RA. In mice, Th17 cells differentiate from CD4+CD25- naïve T cells that have encountered antigen with co-stimulation by IL-6 and TGF-β, and survival of Th17 cells is maintained by IL-23. In contrast, when stimulated with TGF-β alone CD4+CD25- naïve T cells differentiate into T regulatory cells (Treg) that modulate the immune response. Th17 cells produce the inflammatory cytokines IL-17 and IL-22. In this study we aimed to investigate the regulation of Th17 development in human RA patients. We found that peripheral blood mononuclear cells (PBMC) isolated from RA patients produce less Tregs than, but similar IFN-γ and IL-17 levels to PBMCs isolated from healthy donors in response to potent pro-Th17 stimulation. In humans, Th17 cell development requires co-stimulation with IL-6 and IL-1, but not with TGF-β. We found that synovial fluid of the affected joints of RA patients contain higher concentrations of IL-1β, IL-6, IL-23, and TGF-β than affected joints in osteoarthritis patients. However, only IL-23 levels are correlated with IL-17 levels in RA synovial fluid. The methods developed here will be used for further investigation into the development of Th17 cells in RA.
| 11. What was your role in this project? | Experiment performance and data interpretation |
1. **Title**: Educating Healthcare Providers about HIV/AIDS-related Stigma and Discrimination in Uganda

2. **Student Presenter**: Maung Hlaing

3. **Co-workers and Collaborators**: Meghan Gaydos (2), Winny Ngabiirwe (2), Sabrina Eagan (1, 2), and Denis Sama (2)

4. **Advisor**: Joyce Fitzpatrick, Ph.D., R.N., F.A.A.N. (1); Nelson Musoba, M.D. (2)

5. **Departments**: Frances Payne Bolton School of Nursing (1)

6. **Institutions**: Case Western Reserve University (1); Action Group for Health, Human Rights, and HIV/AIDS (AGHA) – Uganda (2)

7. **Support**: Crile Fellowship

8. **Please choose your academic program**: MD

9. **What year are you in the program?**: 2

10. **Body of Abstract (300 words or less)**

    Human rights violations, specifically stigma and discrimination (S&D) by healthcare providers, create a formidable social barrier that prevents those most vulnerable to HIV/AIDS from diagnosis and treatment. Many health workers are unaware of discriminatory behaviors and unknowingly keep patients from seeking and receiving treatment. In Uganda significant efforts to reduce S&D have been made by state and non-governmental organizations. Nevertheless discrimination in all aspects of life prevents many individuals from receiving proper treatment. Very little literature exists on training healthcare professionals (HCP’s) working with HIV/AIDS patients on the social issues of human rights and discrimination. Therefore, we attempted to identify issues most relevant to HCP’s in Uganda in order to provide S&D awareness training.

    The project consisted of two parts. First, we performed a review of human rights literature as well as a review of regional HIV/AIDS literature to determine S&D issues specific to HIV/AIDS in Uganda. We then interviewed several individuals selected for their work with HIV-positive individuals in the healthcare field including an HIV support organization (TASO), a health and human rights organization (AGHA), a traditional healer organization (THETA), and physicians at the national referral hospital (Mulago Hospital) in Kampala, Uganda. The interviewees emphasized four topics: (1) the training needed to be participatory in order to elicit participants’ emotions about HIV/AIDS to help recognize discriminatory behavior; (2) self-stigma amongst HCP’s needed to be addressed; (3) HIV-counseling services need to be provided in healthcare settings; and (4) manuals currently used in S&D training in the community can be adapted for HCP’s. With this information, we began writing guidelines for S&D training. At the end of the summer research period, preliminary guidelines and timelines were being completed.
Currently, pilot training sessions with Ugandan medical students participating as trainees are being undertaken to fine-tune the training protocol.
## Body of Abstract (300 words or less)

Unlike other chronic conditions, in which there are well-established guidelines for routine assessment and follow-up care, guidelines of care for dementia patients are less well defined.

The purpose of this study was to document type and frequency of outpatient care routinely provided as follow-up treatment for patients diagnosed with dementia.

This clinical demonstration project was conducted by geriatric clinicians and researchers at the Cleveland Veterans Affairs Medical Center (VAMC). Approximately 34% of the patients in this interdisciplinary practice have a dementia diagnosis. Using a retrospective design, we abstracted data from the medical records of 62 dementia patients who received follow-up treatment for at least 16 months during 2002-2004. Based on a literature review and clinical experience, we assessed the frequency of documentation of 10 key indicators: Mini Mental Status Exam (MMSE), caregiver strain, patient behavior, ADLs, IADLs, competency, respite needs, referral to Alzheimer’s Association services, driving status, and weapons.

The sample reflected the general geriatric clinic population: 100% male; mean age = 79 (range = 62-87); mean MMSE = 21 (range 4-29). On the initial visit, documentation of the indicators varied from 100% (decision-making) to 3% (Alzheimer’s Association). During follow-up, documentation rates dropped, with mental status most frequently recorded and caregiver needs least frequently recorded. Descriptive and graphical analyses will be used to illustrate major findings. This first phase
of this project provided information about usual care practices in an academic geriatric outpatient clinic. The long-term objective is the development, implementation and evaluation of standard of care guidelines.
### 1. Title
A Statistical Search for a Partner for SLC5A8

### 2. Student Presenter:
Genewoo Hong

### 3. Co-workers and Collaborators:

### 4. Advisor:
Dr. Sanford Markowitz

### 5. Departments:
Hematology & Oncology

### 6. Institutions:
Case Western Reserve University

### 10. Body of Abstract (300 words or less)

- SLC5A8, a plasma-membrane localized sodium transporter, was found by the Markowitz research group to be silenced, via methylation, in a significant fraction of colon cancer cell lines, and is a potential tumor suppressor in colon cancer. The Markowitz lab has observed that, in three cell lines it studied where SLC5A8 was silenced, transfection with SLC5A8 suppressed colony growth, whereas in three cell lines where SLC5A8 was expressed, transfection with SLC5A8 showed no suppressive effect. The existence of a partner tumor suppressor was hypothesized, such that both SLC5A8 and the partner were necessary for non-neoplastic functioning and where silencing of either was tumorigenic.

This study analyzed Affymetrix Exon Array expression data, looking for genes that, judging by their expression pattern, might be a partner for SLC5A8, using a simple comparison of median expression levels in SLC5A8-off tumor cell lines to those in SLC5A8-on tumor cell lines, and using a Spearman rank correlation, followed by FDR. Initially, PDZ-domain proteins, which function as chaperones for transporters being localized to the plasma membrane, were analyzed. The analysis was then broadened to all the genes in the expression data. By Spearman rank correlation followed by FDR, no genes showed a statistically significant inverse expression relationship with SLC5A8-silencing. Of genes studied showing an inverse expression relationship with SLC5A8, the pattern shown by SLC38A5, an amino acid transporter, though statistically insignificant by FDR, may merit further study. That no gene emerged from the statistical analysis as a clear candidate for being partner to SLC5A8 is partly a function of the large number of genes analyzed, which raises the probability of apparent inverse correlation being due to randomness, and consequently raises the bar that must be met for statistical significance.
| 11. What was your role in this project? | Analyst |
Studies have shown that the risk for insulin resistance and diabetes is greatly increased in the obese. One type of treatment to bring about weight loss is bariatric surgery, which is performed on patients who are morbidly obese. The purpose of this study was to examine the changes that occur in body tissue composition following Roux-en-Y gastric bypass surgery. We utilized DEXA scans, measurements of body weight, body height, body mass index (BMI) and waist-to-hip ratio (WHR) to trace the changes that occurred from the pre-op to 6-months to 1-year following surgery. DEXA scans allowed us to calculate the changes in percent Fat Mass (FM) and percent Lean Body Mass (LBM) in various body regions of interest (e.g. arms, legs, trunk, android, and gynoid regions). We found that following RYGB, there was a 35% reduction in BMI after one year, while the WHR decreased from 0.89 to 0.82 (both significant at p<0.05). In the first six months after surgery, FM loss and LBM loss were about equal and amounted to 18.3 kg and 19.5 kg, respectively. In the second six months after surgery, FM loss (9.6 kg) was greater than LBM loss (1.9 kg, p<0.01). Overall, in the cumulative 1-year period, FM loss (27.9 kg) was greater than LBM loss (21.5 kg). Interestingly, the greatest percent FM loss and LBM loss occurred in the trunk and the legs. These findings have raised some interesting issues that must be addressed when considering bariatric surgery. Wouldn’t it be ideal if following weight loss surgery, patients could only lose FM and not so much LBM? We need to design methods--nutritional, exercise, or otherwise--to enhance loss of FM and diminish loss of LBM. Also, since most of the LBM losses in the first year occur mostly in the trunk and legs, we need to design exercise protocols to enhance LBM preservation. Future studies could determine whether interventions such as strength training could diminish loss of LBM in those areas.
**Title**
The role of eIF2A in IRES-mediated translation initiation

**Student Presenter:**
Nasheed M. Hossain

**Co-workers and Collaborators:**
Lucas Reineke and Diane Baus

**Advisor:**
Dr. William Merrick

**Departments:**
Dept. of Biochemistry

**Institutions:**
CWRU School of Medicine

**Support:**
NIH NIGMS Grant GM068079 – Yeast eIF2A: A suppressor of internal initiation, William C. Merrick PI, 01/01/2004-12/31/2007

**Please choose your academic program:**
MD

**What year are you in the program?**
2

**Body of Abstract (300 words or less)**
Internal Ribosome Entry Sites (IRES) are regions of RNA within mRNA molecules that facilitate initiation of protein synthesis independent of the M7G cap at the 5’ end of the mRNA. These sites vary in length, but range between 300 and 1000 nucleotides. Recent work has lead to the observation that yeast translation initiation factor eIF2A can act as a suppressor of IRES-mediated translation at the URE2 IRES.

The focus of this project was to expand our understanding of the role played by eIF2A within eukaryotic cells, specifically yeast cells. We hypothesize that eIF2A exerts its inhibitory effect on IRES-mediated translation by interacting with other proteins within the cell.

Initial work utilized a “pull-down” assay, using a lysate from eIF2A knockout yeast cells transformed with a HA-tagged eIF2A vector. Proteins that bind eIF2A were isolated using an HA-affinity matrix. Proteins were resolved by SDS-PAGE and identified by mass spectrometry. Elution of eIF2A with synthetic HA peptides followed by gel electrophoresis.

The goal of the second phase was to verify interactions identified from the pull down assay by constructing tagged proteins for use in coimmunoprecipitations. The proteins were tagged in two ways. First, proteins were tagged within the yeast cell by homologous recombination of cassettes containing the tag and selectable markers. Subsequently, a GST-eIF2A yeast shuttle vector was created for co-immunoprecipitations from the new yeast strains described above. Second, proteins were GST-tagged using restriction enzymes and an E. coli expression vector to facilitate expression and further pull-down analysis.
The initial pull-down assay highlighted a number of prospective interactions with eIF2A. Specific protein interactions we chose to focus on included those involving SSB2, TEF1, NPL3, KEM1 and DED1. Subsequently, we were able to create and verify strains in which each of the above candidate proteins were HA-tagged. Furthermore, the yeast shuttle vector containing GST-eIF2A was created. Finally, each of the above proteins and eIF2A were inserted into an E. coli expression vector to enable easy expression and verification of the observed interactions.

Based on our initial pull-down assay, it appears that eIF2A does interact with a significant number of other proteins within yeast. In the future, my work will enable the verification of these interactions in several ways. Importantly, the lab will be able to verify these interactions without over-expression of interacting partners, which often leads to false positive results.

| 11. What was your role in this project? | Student Researcher |
1. **Title**  
Attitudes and Perspectives on End of Life Care among Cleveland's Homeless

2. **Student Presenter:**  
Evan Howe

3. **Co-workers and Collaborators:**  
Anthony D'Eramo, Julia Rose

4. **Advisor:**  
Elizabeth O'Toole

5. **Departments:**  
Department of Medicine

6. **Institutions:**  
MetroHealth Medical Center

7. **Support:**  
Crile Fellowship, AFAR Grant

8. **Please choose your academic program:**  
MD MPH

9. **What year are you in the program?**  
2

10. **Body of Abstract (300 words or less)**  
The homeless population represents a unique patient group that is often not able to access health care resources to the same degree as other groups within a population. It is important to understand the unique needs and desires of this population that often has little voice in the debate over just distribution of health care resources. This qualitative study was intended to pursue the attitudes of homeless individuals towards end of life (EOL) care. Currently little research seeks to understand the interests of homeless and shelter dwelling individuals with regard to EOL care. The goal of this study was to determine the amount of knowledge and the interests of the homeless population in this area. A series of focus groups were performed at homeless shelters and drop in centers within the city of Cleveland, Ohio, USA. The questions covered three areas: life values, end of life experiences, and advanced care planning. This data was collected and the transcripts were analyzed using the NVivo software package. The focus groups and interviews highlighted the desire of homeless individuals to receive the same set of health care options as the rest of the population. However, because of the difficulty that this population has in obtaining government assistance to qualify for payment as well as the difficulty in finding a stable residence to receive the care, palliative measures are often not adequately provided. This study shows that while many of the desires of the homeless population in Cleveland, Ohio, USA towards EOL care are the same as the general population, the challenges that face the homeless in order to access EOL care are significantly greater than that encountered by the rest of the population. Special attention needs to be paid to homeless populations to assist them in gaining equal access to health care.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Electrophoretic Evidence That ICBP90 Undergoes Post-translational Modification Upon Hydroxyurea Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Steven Hsu</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Dr. Frank Hong, Shuya Hu, Dr. Frank Un, Dr. Binseng Zhou</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Yun Yen</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Clinical and Molecular Pharmacology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>City of Hope National Medical Center</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>[Background] A transcriptional intervention strategy was developed whereby human cancers resistant to the prototypic antimetabolite drug HU can be eradicated without dose escalation. In eukaryotes, ribonucleotide reductase (RR) inhibition by hydroxyurea (HU) causes deoxyribonucleotide (dNTP) depletion, which activates replication checkpoint. The checkpoint, a component of the S phase checkpoint, responds to DNA damage by executing multiple functions including inhibition of late origin firing, stabilization of replication forks, and blocking of M phase entry. It also triggers transactivation of multiple genes involved in DNA replication and repair such as RR. HU treatment induces RR by increasing transcription of the M2 gene in head and neck cancer. ICBP90 (overexpressed in breast cancer) is a recently identified Rb-associating transactivator for human topoisomerase II alpha gene and responds to DNA damage checkpoint signaling. Recently, we showed that dNTP depletion induces ICBP90, transactivates M2 gene, and that ICBP90 induction is necessary for dNTP depletion-induced M2 accumulation. Furthermore, by abrogating the M2 accumulation via anti-ICBP90 siRNA, greater sensitivity was attained for a HU-resistant human cancer. [Hypothesis] Of interest is the mechanism through which the checkpoint activated by dNTP depletion conveys the signal to ICBP90 to result in M2 transactivation. As ICBP90 was previously shown to be phosphoprotein, it may undergo phosphorylation upon HU treatment by the signaling kinases. [Method] One way to detect it is through observing the difference in electrophoretic mobility as phosphorylation may affect the migration. [Results] Upon electrophoresis through SDS-PAGE, ICBP90 migrates as a single band. When KB human head and neck cancer cells were treated with HU for various times, lysed, electrophoresed and subjected to Western blot analysis, the slowing of the ICBP90 migration occurred.</td>
</tr>
</tbody>
</table>
The data are strongly indicative of that ICBP90 undergoing post-translational modification upon dNTP depletion, setting the stage for next investigation into whether the modification is indeed due to checkpoint-mediated phosphorylation.

11. What was your role in this project?

Researcher
1. Title | NPP1, a Physiological Inhibitor of Calcification, in Human Pulmonary Artery Smooth Muscle Cells
---|---
2. Student Presenter: | Michael L. Hudson
3. Co-workers and Collaborators: | Domenick A. Prosdocimo
4. Advisor: | George R. Dubyak, Ph.D.
5. Departments: | Department of Physiology and Biophysics
6. Institutions: | Case Western Reserve University
7. Support: | This research was conducted with support from the Crile Summer Research Fellowship at Case Western Reserve University offered by the Dean's Office of Case Western Reserve University School of Medicine, the Crile Research Endowment, and NIH grant HL18708 (G. Dubyak, PI).
8. Please choose your academic program: | MD MS
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | Nucleotide pyrophosphatase/phosphodiesterase 1 (NPP1) is a type-II transmembrane ectonucleotidase that acts as a physiological inhibiter of calcification by increasing extracellular pyrophosphate (PPi) in connective tissue matrices. This increase in extracellular PPi is opposed by the hydrolysis of PPi to phosphate (Pi) by the GPI-anchored ecto-alkaline phosphatase (ALP). Studies have shown that macrophages activated by T cell-derived cytokines such as interferon-γ (IFN-γ), in the presence of 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3), increase expression of ALP in human vascular smooth muscle cells (hVSMCs) through production of inflammatory mediators, specifically tumor necrosis factor-α (TNF-α) and oncostatin M (OSM). Since calcification homeostasis is influenced by regulation of NPP1 and ALP through the dynamic interplay of PPi and Pi, we hypothesized that macrophage-induced increases in ALP expression would be associated with increased NPP1 activity. To test this hypothesis, we cocultured human pulmonary artery smooth muscle cells (hPASMCs) and human monocytes (THP-1) for 4 days in the presence of IFN-γ and 1,25(OH)2D3. ALP activity was measured by a colorimetric assay of whole cell lysate using a microplate spectrophotometer. NPP1 activity was assayed by the metabolism of fluorescently-derived Sβ-MeATP (Sβ-MeATP) via HPLC. Cocultures of hPASMCs and THP-1 cells treated with IFN-γ and 1,25(OH)2D3 showed no increase in NPP1 activity when incubated with Sβ-MeATP for 1 hour. We also did not observe an increase in ALP or total phosphodiesterase activity in the treated cocultures. Further analysis of the hPASMC cultures indicated reduced levels of a-smooth muscle actin when compared to 1° rat aortic smooth
muscles cells. We speculate that the absence of predicted increases in NPP1 activity can be explained by loss of 1º smooth muscle phenotype in our relatively high passage (p. 13) hPASMCs. Additional studies are necessary to determine whether ALP upregulation in smooth muscle cells occurs concomitantly with increased NPP1 activity.

11. What was your role in this project?  

Researcher
1. Title

Punica granatum L. extract inhibits IL-1beta induced activation of p38-mitogen activated protein kinase and suppresses IL-1beta induced expression of ICAM-1 in Human Umbilical Vein Endothelial Cells in vitro

2. Student Presenter:

Eun Huh

3. Co-workers and Collaborators:

Meenakshi Shukla, Kalpana Gupta

4. Advisor:

Dr. Tariq Haqqi

5. Departments:

Medicine - Rheumatology

6. Institutions:

Case Western Reserve University

7. Support:

8. Please choose your academic program:

MD

9. What year are you in the program?

2

10. Body of Abstract

(300 words or less)

Background: Inflammatory cytokines produced by activated macrophages in the synovium have been identified as the major inducers of endothelial cells (EC) activation in rheumatoid arthritis (RA). Activated EC lining the blood vessels produce a number of inflammatory mediators and express cellular adhesion molecules (CAM). The expression of the adhesion molecules is central to the attachment of leukocytes to the endothelium and secreted chemokines then direct transendothelial migration of activated leukocytes to the site of inflammation. Decrease in inflammatory cytokine production and decreased expression of E-selectin and ICAM-1 have been shown to be associated with improved joint function and disease remission.

Human umbilical vein endothelial cells (HUVEC) upregulate the expression of selectins when stimulated by IL-1? in vitro. p38-mitogen activated protein kinase (p38-MAPK) has been shown to be an important regulators of CAM expression, targeting p38-MAPK is emerging as a novel therapeutic approach for the treatment of various inflammatory disorders. Our lab has previously shown that an extract of pomegranate fruit (PFE) was highly effective in suppressing the cytokine-induced activation of p38-MAPK in human chondrocytes. In this study we set out to determine whether PFE will suppress the IL-1?-induced activation of p-38 MAPK and whether PFE will suppress the IL-1?-induced upregulation of adhesion molecules E-Selectin and ICAM-1 in HUVEC in vitro.

Methods: HUVEC were pretreated with PFE at different concentrations (10-200 ?g/ml) for 90 minutes then stimulated with IL-1beta (2 and 5 ng/ml) for 60 minutes, 6 and 24 hours. Expression of E-selectin and ICAM-1 was quantified using flow cytometry. The expression and
phosphorylation of p38-MAPK was determined by Western immunoblotting.

Results: The HUVEC used, from Cambrex Corporation, did not express E-selectin. At high PFE concentrations (200 μg/ml) IL-1β-induced expression of ICAM-1 was inhibited (5-20%). The same dosage of PFE was highly effective in suppressing the IL-1β-induced phosphorylation of p-38 MAPK in HUVEC.

Conclusions: PFE or its metabolites may be beneficial in treating inflammatory activation of EC by suppressing phosphorylation of p38-MAPK and the expression of ICAM-1.
## 1. Title
Community-Acquired vs. Nosocomial Intra-abdominal Infections: a Retrospective Review of Origin and Outcome

## 2. Student Presenter:
Tazo S. Inui

## 3. Co-workers and Collaborators:

## 4. Advisor:
Dr. Mark A. Malangoni

## 5. Departments:
Department of Surgery

## 6. Institutions:
Metrohealth Medical Center

## 7. Support:
NIH T-35

## 8. Please choose your academic program:
MD

## 9. What year are you in the program?
2

## 10. Body of Abstract (300 words or less)
BACKGROUND: While nosocomial secondary peritonitis and intra-abdominal infections (IAIs) are assumed to be associated with greater morbidity and mortality in the surgical patient, little research has compared nosocomial IAIs with community-acquired (CA) IAIs. HYPOTHESIS: the aim of this retrospective chart review was to determine if more negative outcomes are associated with nosocomial IAIs seen and surgically treated at a large, urban, tertiary care center between 1999 and 2006. METHODS: Using a combination of ICD-9 CM codes, the electronic health records of patients who were classified as having a disease state associated with secondary peritonitis and who had undergone a surgical intervention (either via operation or radiologically-guided drainage) were analyzed for etiology of disease, intervention, associated flora, and outcome. Primary endpoints included mortality, PE/DVT, MI/arrhythmia, the need for re-operation or re-drainage. Secondary endpoints included: days in ICU, greater than 72 hrs on assisted ventilation, and associated infection (e.g. sepsis, pneumonia, UTI, additional IAIs/pelvic abscesses). RESULTS: There are currently 246 patients who meet the above criteria. Twenty-eight patients were diagnosed with nosocomial IAIs. Four of the patients with nosocomial IAIs (14%) died during the course of hospitalization, compared with 6 of the patients with CA IAIs (2.7%). Seven patients suffered MIs (5 CA IAI, 2 nosocomial); 10 had arrhythmias (5 CA IAI) after surgical intervention. 5 DVTs were reported (3 CA IAI). Sixteen of CA IAIs (7%) returned to the OR once; 15 (6.8%) required additional CT-guided drainage. Nine patients with nosocomial IAIs (32%) returned for re-exploration in the OR; 7 (25%) required additional CT-guided drainage. CONCLUSION: There is substantial additional morbidity and mortality for patients who acquire nosocomial IAIs. Further research is warranted to more precisely determine causative factors, and
to identify potential avenues for reducing the risk of nosocomial IAI.

| 11. What was your role in this project? | student investigator |
Objective: To investigate factors related to food insecurity in poor urban households in three areas of Johannesburg, South Africa. Methods: A baseline survey was conducted in 150 households across three poor regions of the city of Johannesburg: Diepsloot, Orange Farm, and Joubert Park. Each region was divided into five sections, and ten randomly sampled households were interviewed for each section. Respondents provided an overview of their entire flat or yard, and gave more detailed information for one household per flat, including food security, livelihood activities, socioeconomic status and changes, and social support. Food security, measured by a scale developed by Radimer and colleagues, was compared to several variables reflecting social vulnerability. Results: The overall prevalence of food insecurity was 64.8%. Households were more likely to be food insecure if they had experienced any big events or changes in the past year that decreased the economic welfare of the household (p=0.002), if they had at least one member requiring special support (p=0.001), and if they had more household members (p=0.046). Increased household wealth (p=0.009), possession of more consumer goods (p<0.001), having at least one employed household member (p=0.008), and having more employed members (p=0.011) were associated with greater food security. Conclusion: Several factors reflecting financial insecurity and social vulnerability were associated with food insecurity.
| 11. What was your role in this project? | First author |
1. Title
The Distribution of Calsequestrin in the rat brain

2. Student Presenter:
Sogol Javaheri

3. Co-workers and Collaborators:
Zhen-zhen Wu and Dale Feng

4. Advisor:
Dale Feng and Kingman Strohl

5. Departments:
Pulmonary

6. Institutions:
VA Medical Center

7. Support:
Crile T35 scholarship

8. Please choose your academic program:
MD

9. What year are you in the program?
2

10. Body of Abstract (300 words or less)
Calsequestrin is the most abundant Ca2+-binding protein in the sarcoplasmic reticulum of skeletal and cardiac muscle and also exists in the brain. Our preliminary data demonstrated that when compared to age-matched rats in usual cage conditions, juvenile rats given the opportunity to exercise (wheel running) for six weeks show an increase in frontal cortical and hippocampal levels of calsequestrin-2 but not calsequestrin-1. However, there is no data about how these proteins are distributed in the brain and the neurons. We proposed to map these proteins in the entire brain in the rat by immunohistochemistry. 4 rats were killed by transcardiac perfusion with 4% paraformaldehyde in PBS buffer. Brains were removed, processed with 30% sucrose and then coronal sections were cut at 30 µ. Sections were blocked with animal serum, incubated with rabbit antibody against calsequestrin-1 and goat antibody against calsequestrin-2 and then with secondary goat antibody against rabbit and secondary horse antibody against goat. Then standard ABC procedure provided by the Vector’s Lab was followed, and positive stained cells were revealed by the DAB method from the same company. Sections were mounted on slides and viewed under a light microscope. Preliminary results indicate that cells positively stained by antibodies against both calsequestrin-1 and 2 existed in the brain tissue. Cell positively stained by calsequestrin-2 are much more abundant than that of calsequestrin 1. These cells distributed thoroughly in the cortex, hippocampus, and brain stem. In the cortex most cells are in grey matter and in deeper layers such as layer IV. This implicates that the proteins coexist with neurons but not glial cells. However, characterizing the distribution of these proteins with double staining technique is needed. We plan to double-label both calsequestrin-1 and 2 with other enzymes and to use electron microscopy technology to further study these proteins.
11. What was your role in this project? | Extracting the rat brains, slicing them, staining them, and analyzing the data using a light microscope.

1. Title | Increased Blood Pressure In Adolescents with Poor Sleep Quality

2. Student Presenter: | Sogol Javaheri

3. Co-workers and Collaborators: | Storfer-Isser A1, Rosen CL,2 Johnson NL1, Redline S1

4. Advisor: | Susan Redline

5. Departments: | Center for Clinical Investigation1 Department of Pediatrics2

6. Institutions: | Case Western Reserve University

7. Support: | 

8. Please choose your academic program: | MD

9. What year are you in the program? | 3

10. Body of Abstract (300 words or less) | Introduction: Adolescents are at high risk for insufficient sleep, a risk factor for behavioral morbidity and obesity. Although short sleep duration has been reported to increase the risk of hypertension among adults, it is unknown whether insufficient sleep is associated with high blood pressure (HBP) in healthy adolescents. Methods: 238 adolescents without sleep apnea (apnea hypopnea index < 5) from the Cleveland Children’s Sleep and Health Study. Subjects underwent 5-7 day wrist actigraphy, overnight polysomnography (PSG), anthropometry, and 9 blood pressure (BP) measurements. The exposures were low weekday sleep efficiency (low SE: <85%) and short sleep on weekdays (<6.5 hrs) from actigraphy; outcome variables were HBP (>90th%ile for age, sex, and height), systolic BP (SBP), and diastolic BP (DBP). Logistic regression models were adjusted for sex and BMI percentile (BMI%); multiple linear regression models were adjusted for age, sex, race, preterm status, and BMI%. Results: Subjects were 13.7 ± 0.7 (mean ± SD) years; 52% male; 55% minority; 14% HBP, 26% low SE and 11% short sleep. In adjusted analyses, adolescents with low SE had nearly a 4-fold increased odds of HBP (OR=3.98, 95% CI: 1.80. 8.77) and had 3.9 ± 1.2 mmHg higher SBP on average (p<0.01). Short sleep was marginally associated with increased odds of HBP (OR=2.60, 95% CI: 0.97, 7.02) and was not significantly associated with SBP in adjusted analyses. Neither exposure was associated with DBP. Similar findings were obtained when low SE was derived from overnight PSG.
Conclusions: Poor sleep quality is associated with HBP and increased SBP in this sample of adolescents without sleep apnea. The strong association between low SE and BP in a young and otherwise healthy sample provides further support that disturbed sleep has a putative role of in the pathogenesis of hypertension.

| 11. What was your role in this project? | Literature search, data analysis, writing |
The purpose for the project was to employ an oligonucleotide ligation assay that was developed by Dr. Arts and his lab. This assay is unique in that as compared to the genotypic and phenotypic approaches currently employed, it is believed that mutant virus can be detected up to a sensitivity of 0.5% as compared to the current 20%.

To address the project more specifically, the hope was to characterize NNRTI-associated mutations by single nucleotide polymorphism analysis of clinical samples obtained from a cohort of mother-child pairs in which the mothers received a single dose of nevirapine to prevent mother-to-child transmission of the virus. The mutations to be probed for were the K103N and the Y181C mutations as these are the first mutations usually seen in clinical NVP drug resistance. How drug-resistant virus is maintained over time was also hoping to be studied. The results of this second component are of course as yet unknown. I may eventually see that these resistance mutations are not fit and disappear as more competent viruses are permitted to outgrow them in the presence of drug pressure. This would be manifested in the disappearance of the drug-resistance mutations at different timepoints.
1. Title | Planning for Rift Valley Fever: Use of GIS to estimate the human health threat of White-tailed deer (Odocoileus virginianus)-related arbovirus transmission in an urban-suburban environment in Northeast, Ohio, USA

2. Student Presenter: | Sravan Kakani

3. Co-workers and Collaborators: | 

4. Advisor: | Charles H. King

5. Departments: | Center for Global Health

6. Institutions: | Case Western Reserve University

7. Support: | T-35 Short-term Research Training Grant

8. Please choose your academic program: | MD MPH

9. What year are you in the program? | 2

10. Body of Abstract (300 words or less) | In bioterrorism, the introduction and accelerated spread of highly pathogenic viruses in naïve populations could incapacitate or kill large numbers of susceptible animals and people. This paper discusses the zoonotic and vector abundance factors likely to be involved in determining the areas of highest risk for an outbreak of an exotic pathogen, Rift Valley Fever Virus (RVFV) within Cuyahoga County, located in the northeastern part of the state of Ohio, USA. Our objective is to begin the formulation of likely threats, and to map out areas for initial prioritization for public health interventions that will most effectively restrict transmission of RVFV. Analyses were performed using ArcGIS version 9.2. Based on the features of zoonotic spread likely to occur in the local environment, we examined ecological variables that included 1) measured density of June/July or August/September Culex and Aedes vexans mosquito species; 2) measured density of human population; and 3) projected pre- and post-culling density estimates for White-tailed deer. For each variable, density raster maps were created and density values were divided into ten equal intervals. Raster calculator was used to evaluate all three raster density maps simultaneously. A risk threshold was set above the second decile for all variables to evaluate their spatial intersection. Preliminary results suggest that geographic overlap of mosquitoes, humans, and deer occurs in the periphery of Cleveland proper for the June/July period. This region appears to extend into contiguous municipalities for the August/September period. It is expected that health planners can use such pre-formulated “temporal risk maps” to identify when and where control measures should be targeted spatially to reduce transmission in the event of an outbreak.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11. What was your role in this project?</strong></td>
<td>main researcher</td>
</tr>
<tr>
<td>1. Title</td>
<td>Carbapenems Form Different Acyl-Enzyme Populations in Crystals and Solutions of the β-Lactamase SHV-1</td>
</tr>
<tr>
<td>----------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Matthew Kalp</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Robert A. Bonomo, MD</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Paul R. Carey, PhD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Biochemistry</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>School of Medicine, Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>4</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>The reactions between single crystals of the SHV-1 β-lactamase and the carbapenems, meropenem, imipenem and ertapenem, have been studied by Raman microscopy. Aided by quantum mechanical calculations, major populations of two acyl-enzyme species, a labile Δ2-pyrroline or a more tightly bound Δ1-pyrroline, have been detected for all three compounds. These isomers differ only in the position of the double bond about the carbapenem nucleus. This discovery is consonant with the X-ray crystallographic findings of Nukaga et al. who also identified two populations for meropenem bound in SHV-1: one with the acyl center in the oxyanion hole and the second with the acyl group rotated 180 degrees compared to its expected position. When crystals of the Δ1 and Δ2 containing acyl-enzymes were exposed to solutions with no carbapenem, rapid deacylation of the Δ2 species was observed by kinetic Raman experiments. However, no change in the Δ1 population was observed over 1 hour, the effective lifetime of the crystal. These observations lead to the hypothesis that the stable Δ1 species is due to the form seen by X-ray with the acyl carbonyl outside the oxyanion hole, while the Δ2 species corresponds to the form with the carbonyl inside the oxyanion hole. Soak-in and soak-out Raman experiments also demonstrated that tautomeric exchange between the Δ1 and Δ2 forms does not occur on the enzyme. When meropenem or ertapenem were reacted with SHV-1 in solution the Raman difference spectra demonstrated that only a major population corresponding to the Δ1 acyl-enzyme could be detected. Here, we provide strong evidence that the Δ1 and Δ2 acyl-enzymes are present in approximately equal amounts in the crystal, in agreement with the X-ray data. However, in solution there is twice as much Δ1 and this represents approximately 100% of the active sites leading to effective inhibition of the enzyme's activity.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Experimentor</td>
</tr>
</tbody>
</table>
**KAN, CHARLENE**

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Mammary Epithelial Cells Transformed by Cyclin-Dependent Kinase Hyperactivity are Partially Sensitized to p53-mediated Arrest in Response to Nutlin-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>CE Kan</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>MW Jackson</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>GR Stark</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Genetics and Department of Molecular Genetics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University, Case Comprehensive Cancer Center and The Cleveland Clinic Foundation, Lerner Research Institute</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH RO1 funding to George Stark</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>4</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Cyclin D1, a key cell cycle regulator, initiates cell cycle progression from G1 to S phase by complexing with cyclin-dependent kinases (CDK) to promote the phosphorylation of RB and therefore E2F-dependent transcription. Overexpression of cyclin D1 is frequently observed in breast carcinomas and expression of constitutively active cyclin D1 has been shown to transform mink epithelial cells in vitro. We show here that CDK hyperactivity transforms immortalized human mammary epithelial cells (HMECs) independently of p53 inactivation, but that cells retaining p53 activity remain relatively sensitive to cellular arrest induced by Nutlin-3, an Hdm2 antagonist that stabilizes p53. Cells lacking p53 were resistant to Nutlin-3 regardless of cyclin D1/cdk status. Regarding cells containing functional p53, control cells exhibited a decrease in phosphorylated RB upon Nutlin-3 treatment, while D1/cdk expressing cells maintained phosphorylated RB levels. This indicates that there exist additional RB-independent mechanisms for cdc2 down regulation. Following removal of Nutlin-3, cdc2 remained suppressed in both control and D1/cdk-expressing cells. We conclude that the D1/cdk complex is able to disrupt the necessary pathways in order to cause transformation in vitro; however, the p53 pathway can still be activated to cause cellular arrest as evidenced by the partial resistance to Nutlin-3 treatment. This indicates that compounds such as Nutlin-3 which activate the p53 signaling pathway may be effective in breast cancers which over express cyclin D1 but still have wild type p53 signaling.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Conducted most of the research</td>
</tr>
</tbody>
</table>
Evaluation of Trauma Team Activation Protocol at a Level I Trauma Center

Justin Kan

Patricia Wilczewski, RN

Jeffrey Claridge, MD

Department of Surgery, Division of Trauma, Burns, and Critical Care

Metro Health Medical Center

Crile fellowship, MetroHealth Department of Surgery Funds, and Dr. Claridge is supported in part by the National Institutes of Health, National Institute of Child Health and Human Development, Multidisciplinary Clinical Research Career Development Programs Grant K12 HD049091

MD

2

Background:
There are criteria that are used to trigger trauma team activation based on prehospital assessment of trauma patients. These trauma activations involve the mobilization of a health care team and utilization of a large amount of resources. Patients who require trauma activations are thought to need rapid assessment, potential intervention, and presumed admission to the hospital at a priority above other patients.

Hypothesis:
Certain criteria are not associated with the necessity of trauma activations.

Methods:
A prospective observational study was performed at a level one trauma center on all trauma activations between August 1, 2005 and January 31, 2006. Data collected included mechanism of injury, trauma activation criteria, age, gender, disposition, and patient identifiers. Specific Trauma team activation criteria were evaluated to identify which criteria were associated with admission.

Results:
2067 patients were evaluated with the average age of 37.5 years. 70% were male and 87% of patients suffered blunt injury, of which motor vehicle crashes were the most common mechanism. The two most common single criteria were Glasgow Coma Score (GCS) of 12–14 seen in 27% of patients and a reported high speed motor vehicle crash (MVC >
45 mph) seen in 37.5% of patients. There was no association between GCS of 12 – 14 with admission. In patients with a GCS of 12-14, 27% were admitted and 25% were discharged (p=0.36). There was a significant inverse association between MVC > 45 mph and admission. In patients with a MVC > 45 mph, 26% required admission and 39% were discharged (p<0.001).

Conclusions:
Despite the most common reasons for trauma activations, a GCS of 12-14 had no association with admission, and MVC >45 mph had an association with discharge from the hospital. Thus, patients with one of these two criteria could be a target population to decrease resource allocation.

| 11. What was your role in this project? | Collection of data, data analysis, and development of proposal for procedure change, writing abstract, and preparation of manuscript. |
1. **Title**: Cognitive and Behavioral Functioning in Children with Congenital Heart Disease: A Pilot Study

2. **Student Presenter**: Yu Kawai

3. **Co-workers and Collaborators**: None

4. **Advisor**: Dr. Patricia Klaas and Dr. Lourdes Prieto

5. **Departments**: Children's Hospital - Congenital Heart Disease

6. **Institutions**: Cleveland Clinic

7. **Support**: None

8. **Please choose your academic program**: MD

9. **What year are you in the program?**: 2

10. **Body of Abstract (300 words or less)**: Children with congenital heart defects are more likely to experience acute or chronic hypoxia, especially for those who receive cardiac repair surgery, compared to children without congenital heart malformations. The hippocampus is vulnerable in hypoxic or anoxic events often resulting in memory and cognitive difficulties. Hypoxemia may also result in academic, emotional, and behavioral difficulties in children. However, no known studies have systematically investigated these factors as they pertain to children with congenital heart defects who have required cardiac repair surgery. Our primary goal is to investigate the long term effects of congenital heart defects on cognitive and behavioral functioning in children ages 6-16 who have undergone surgical intervention compared to those with congenital heart malformations who have not had any surgical intervention. The patients will be evaluated based on results from the Conner’s Parent Rating Scale – Revised (S), Achenbach Child Behavior Checklist for Ages 6-18, and history questionnaire concerning early childhood development, medical history, and academic placement. The study is on-going and the data is currently being collected. It is anticipated that parents of children who required cardiac repair surgery will report greater cognitive and behavioral difficulties than those of children with cardiac conditions that have not undergone surgery. The effect of chronic cyanosis will also be evaluated by comparing children who have required cardiac surgery for cyanotic versus acyanotic heart disease. It is anticipated that children with cyanotic heart disease requiring surgery will demonstrate a higher likelihood of cognitive and behavioral difficulties on these measures than children with acyanotic heart disease requiring surgery. It is hoped that information obtained from this study will assist in developing a better understanding of the cognitive and behavioral sequelae of congenital heart defects and their surgical intervention in children and
the development of early interventions aimed at reducing cognitive and behavioral difficulties.

<p>| 11. What was your role in this project? | Secondary Student Investigator |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Accuracy analysis of an image-guided system for vertebroplasty based on electromagnetic tracking of instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Noureen Khan</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Jayson Ding, Patrick Cheng, Emmanuel Wilson, Corey Gibson, Vance Watson, Kevin Cleary</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Kevin Cleary, PhD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Imaging Science and Information Systems (ISIS) Center, Department of Radiology, Georgetown University Medical Center, Washington, DC, 20007, USA</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>School of Medicine, Case Western Reserve University, Cleveland, OH, 44106, USA Dept. of Radiology, Georgetown University, Washington, DC, 20007 USA</td>
</tr>
<tr>
<td>7. Support:</td>
<td>The Case Western Reserve School of Medical under the Crile Grant for funding Noureen Khan’s research. Imaging Science and Information Systems (ISIS) Center, Department of Radiology, Georgetown University Medical Center, Washington, DC, 20007 USA</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Purpose: The purpose of this study was to validate and determine the accuracy of an electromagnetic image tracking system used for trocar needle guidance during vertebroplasty. We compared the accuracy of hitting a predetermined target with EM guidance technique by comparing the reported EM guidance error and the actual error calculated using a fluoroscopy image. Additionally, the accuracy with EM guidance is compared between operators of varied experience levels. 

Methods: Using phantoms with sawbone spines vertebroplasty was performed 10 times each by 1) radiology interventionalist 2) practicing fellow and 3) 2nd year medical student on vertebrae bodies T1 to L3 spine. The software tracks needle positioning in order to display the most ideal pathway to display three key points; a) trocar insertion point on skin; b) trocar insertion point on vertebrae bone; c) trocar target point. The navigation system displays off-axial, off-sagittal, and coronal views to allow for maximum efficiency of needle insertion. A single fluoroscopy image is taken to confirm needle placement. The trocar tip point is compared with the inserted fiducial target point to determine accuracy.

Results: Of the total 30 trials, the average actual error was $2.44 \pm 1.23$mm with a
time of 2:35 ± 1:12min. The average EM guidance error for all 30 trials was 2.56 ± 1.29mm. There is a clear relationship between the level of training experience and accuracy. The mean range for the radiology interventionalist was trocar needle placement 1.90 ± 0.66mm away from the target point; the fellow 2.29 ± 1.26mm; and the MSII 3.13 ± 1.38mm. The attending completing the trials in the shortest amount of time with an average of 1:39± 0:39 minutes; the fellow averaged 2:57 ± 1:19 minutes; the longest average time of 3:08 ± 1:07 minutes belongs to the medical student.

Discussion:
Using IGSTK EM image guidance, we have successfully and accurately placed trocar needle within the desired vertebrae within an average of less than 4 mm accuracy and in an average of less than 4 minutes with three wide-ranging levels of experienced operators. This new technique proves to have equivalent accuracy as fluroscopic image guidance within a more rapid amount of time and less radiation exposure to patient and physician. Further studies will be explored in clinical trials.

11. What was your role in this project?

I was the intermediate between clinician and scientist on this research, developed the project for this study, participated in 10 of the experimental trials, observed surgical vertebroplasty, and wrote the manuscript and abstract. The abstract, where I am second author, has been submitted and accepted to SPIE Symposium on Medical Imaging which will be held 16-21 February, 2008 in San Diego, CA.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>The role of a single nucleotide polymorphism in the MDM2 promoter in Glioblastoma Multiforme</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Rina Khatri, B.A.</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Kapila Navaratne, M.S., Robert J. Weil, M.D.</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Robert J. Weil, M.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Brain Tumor Institute</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Cleveland Clinic, OH 44195</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Purpose: Glioblastoma multiforme (GBM) is the most common form of primary brain tumor in adults, and has very poor outcomes (5-year survival of &lt;5%). The aggressive behavior of these tumors makes therapeutic intervention both a challenge and a necessity. A better understanding of the molecular alterations in GBM that influence survival and response to therapy is a key step in advancing treatment efficacy. Dysregulation of the p14arf/MDM2/p53 tumor suppressor pathway has been proposed as a potential mechanism by which astrocytic cells undergo malignant transformation. Mutations in p53 have been found in 25-40% of tumors and MDM2 mutations in 10%. MDM2 serves as a negative regulator of p53 through sequestration and ubiquitination of p53. Recently, Bond et al. identified a single nucleotide polymorphism (SNP) in the mdm2 gene which increases the affinity of the promoter for the transcriptional activator Sp1, resulting in increased MDM2 expression and subsequent attenuation of the p53 pathway. This SNP has been shown to influence risk, age of onset and survival in several cancer types; however its role in GBM is unknown. We studied the role of this MDM2 SNP in GBM. Methods: We genotyped 98 GBM patients and 102 normal controls at the MDM2 promoter for the SNP using polymerase chain reaction (PCR). The results were analyzed using GraphPad Prism Version 3.0. Results: We found that GBM patients were more likely than normal control subjects to have the T/G or G/G genotype (p=0.02) and that the frequency of the G-allele was higher in GBM patients than in normal controls (p=0.04). However, we found no correlation between age of onset or survival time and MDM2 genotype.</td>
</tr>
</tbody>
</table>
Conclusion: The G allele is found in higher frequency in GBM patients; however, it does not seem to confer an increased risk or a more malignant course of GBM.

| 11. What was your role in this project? | I established the protocol, performed the experiments and analyzed the data. |
KIDO, MAYA

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Comparing Adverse Post-Discharge Effects of Procedural Sedation Analgesia in Pediatric Emergency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Maya Kido</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Baruch Krauss, Alisa McQueen</td>
</tr>
<tr>
<td>5. Departments:</td>
<td></td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Harvard University, Children's Hospital Boston</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Procedural sedation and analgesia (PSA) is the use of sedative, analgesic and dissociative agents to provide anxiolysis, analgesia, sedation, and motor control for patients undergoing diagnostic and therapeutic procedures. The efficacy and safety of PSA during the procedure and post-procedure prior to discharge periods has been well documented, but adverse effects post-discharge have not been studied. In order to better understand the potential risks associated with PSA in the post-discharge period, this study proposes to examine the adverse events associated with the two most common PSA agents; ketamine and fentanyl/midazolam. Ketamine is associated with emergence delirium while the child is still in the ED, raising questions about the longer term effects post-discharge. With greater understanding of the PSA post-discharge period, physicians may be able to reduce adverse side effects and improve discharge instructions to families. The study will be a prospective, observational cohort of children undergoing PSA in the Children’s Hospital Boston emergency department. Physicians will, independent of the study, determine if patients need PSA and assign an appropriate therapeutic agent. If the physician chooses either ketamine or fentanyl/midazolam the patient will be eligible for enrollment. Among eligible patients, informed consent will be obtained from either the patient or guardian for use of demographic data from the ED medical record and for a follow-up phone call in one week consisting of a validated behavioral questionnaire. Data collection is expected to be completed by June 2007. Once complete, the data will be analyzed comparing the number of maladaptive behaviors exhibited by children receiving either ketamine or fentanyl/midazolam, adjusting for preoperative anxiety and covariates such as subject age, sex, medication use and type/site of injury.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Data Collection, Data Input</td>
</tr>
</tbody>
</table>
Newly developed selective agonists and antagonists have allowed for a closer examination of the 4 major Adenosine receptors (A1, A2A, A2B, A3) and their role in the mechanism of insulin release. Combinations of selective and non-selective adenosine receptor agonists and antagonists were used to measure changes in the amount of insulin secreted by rat pancreatic islet cells. We hypothesized that activation or inhibition of individual subtypes of adenosine receptors would result in differential changes in insulin secretion. Insulin secretion was measured by radioimmunoassay (RIA), using 125I, in the presence of a stimulatory glucose concentration (5.6 mM). NECA (10 µM), a non-degradable adenosine analog, caused an overall increase in insulin secretion. Caffeine, a non-selective AR antagonist, was found to increase insulin release at multiple concentrations (0.1 to 100 µM). CHA (10 µM, A1 receptor agonist) was found to by itself increase insulin release and led to increased secretion when combined with higher concentrations of caffeine. It was thought that specific adenosine-receptor antagonists on their own would have no intrinsic effect on insulin release, but one A2B receptor antagonist, PSB-1115, showed varying effects across a range of concentrations. Adenosine itself, which is quickly degraded, had no effect on insulin secretion at two concentrations (10 and 100 nM). The results indicate that activation of A1 and inhibition of A2B may lead to an overall increase in insulin secretion.
<p>| 11. What was your role in this project? | researcher |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Asthma control and physician agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Peter Knoll</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Rita Cydulka, MD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Emergency Medicine</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>MetroHealth Medical Center</td>
</tr>
<tr>
<td>7. Support:</td>
<td>T32 (HL083823)</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Treatments for asthma are currently based on the severity of the disease. Soon-to-be-published guidelines will emphasize the importance of asthma control as a determinant for asthma treatment alongside severity. With an increased emphasis on asthma control, it is important that the physician accurately assesses his patient's level of control. Our study aims to quantify the level of agreement between the physician's judgment and the patient's level of asthma control in an emergency department setting. Patients with a history of asthma presenting to the MetroHealth Medical Center Emergency Department were administered two validated asthma control surveys - the Mini Quality of Life Questionnaire (MQLQ) and the QualityMedtric Asthma Control Test (ACT). Attending physicians were asked for their assessment after evaluating the patient. According to the ACT, more than 69% of the sample population (n=107) had inadequately controlled asthma. Of these individuals, physicians only identified 47% as inadequately controlled. Physicians rated 16% of those with inadequate control as having adequate control and did not even assess the patient's asthma the other 36% of the time. Among the subset of individuals presenting to the emergency department for something other than an acute asthma exacerbation (n=75), a mere 20% with inadequate control based on the ACT were labeled as such by physicians. Of the remaining 80%, physicians did not address the patient's asthma 56% of the time, and the remaining 24% were incorrectly judged to have adequate control. In order for asthma control to be an effective variable in treatment determination, it is important that physicians accurately assess an individual's level of control. This study, though limited in size and location, shows a very high prevalence of patients with inadequate asthma control going unrecognized.</td>
</tr>
</tbody>
</table>
11. What was your role in this project?

| Interviewing patients and physicians to gather data |
# Outcomes of Extremely Low Gestational Age Infants (ELGA, <28 weeks) with Bronchopulmonary Dysplasia: Effects of Practice Changes in 2000-2003

## 1. Title
Outcomes of Extremely Low Gestational Age Infants (ELGA, <28 weeks) with Bronchopulmonary Dysplasia: Effects of Practice Changes in 2000-2003

## 2. Student Presenter:
Kristen Kobaly

## 3. Co-workers and Collaborators:
Mark Schluchter, PhD; Nori Mercuri-Minich, MA; H. Gerry Taylor, PhD; Deanne Wilson-Costello, MD; Richard Martin, MD; Maureen Hack, MD

## 4. Advisor:
Maureen Hack, MD

## 5. Departments:
Department of Pediatrics

## 6. Institutions:
Case Western Reserve University

## 7. Support:
T35 Short Term Research Training Grant, HL082544

## 8. Please choose your academic program:
MD

## 9. What year are you in the program?
2

## 10. Body of Abstract (300 words or less)

**Objective:** Extremely low gestational age (ELGA, < 28 weeks) infants with Bronchopulmonary Dysplasia (BPD) suffer poorer early childhood cognitive and neurodevelopmental outcomes than preterm and term-born controls. We sought to evaluate whether changes in neonatal intensive care unit (NICU) practices and therapies have improved BPD outcomes.

**Design/Methods:** We compared early childhood outcomes of ELGA infants between two periods: Period I, 1996-1999 (n=118) and Period II, 2000-2003 (n=107). Outcomes included neurosensory abnormalities (cerebral palsy, blindness, deafness), the Bayley Scales of Infant Development Mental Developmental Index (MDI), and overall neurodevelopmental impairment (subnormal MDI and/or neurosensory abnormality). Effects of NICU changes on outcomes were examined via multivariate analyses.

**Results:** NICU changes between period I and II included increased antenatal (72% vs. 83%, p=0.046) and postnatal (75% vs. 29%, p=0.000) steroid therapy, decreased severe cranial ultrasound abnormality (25% vs. 13%, p=0.012), and increased ventilator dependence (36 vs. 43 days, p=0.020). Rates of BPD did not change (52% vs. 53%).

Follow-up at 20 months corrected age revealed fewer neurosensory abnormalities during Period II (36% vs. 16%, p=0.011), but no change in the rates of subnormal (<70) MDI (37% vs. 45%). Overall neurodevelopmental impairment did not change (50% vs. 51%).

Multivariate analyses, including time period (I vs. II) as a variable, revealed significant (p<0.05) predictors of subnormal MDI to be cranial ultrasound abnormalities.
abnormality and duration of ventilator dependence. Predictors of neurodevelopmental impairment included cranial ultrasound abnormality, increased ventilator dependence and postnatal steroid therapy.

Conclusions: Changes in NICU practices have not improved the rates of BPD or its overall outcomes. In fact, infants spend more time on ventilators, possibly due to reduced postnatal steroid use. Further therapeutic modifications are needed to decrease both the rates of BPD and its long-term outcomes.

| 11. What was your role in this project? | I completed a literature review, planned data analysis requirements, interpreted results, and wrote a paper of our findings to be submitted for publication. |
1. Title | Hypofractionated Radiation Treatment in Recurrent Glioblastoma Multiforme
---|---
2. Student Presenter: | Tai Kobayashi
4. Advisor: | Dr. Sam Chao
5. Departments: | Dept of Radiation Oncology at the Cleveland Clinic
6. Institutions: | Cleveland Clinic
7. Support: | N/A
8. Please choose your academic program: | MD
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | Hypofractionated Radiation Treatment in Recurrent Glioblastoma Multiforme


**Purpose/Objective(s):** To determine whether hypofractionated radiation is beneficial in treating recurrences in glioblastoma multiforme.

**Materials/Methods:** After review of Cleveland Clinic’s brain tumor database, 10 patients were identified who received hypofractionated radiation (RT). The following data was obtained for each patient: age at RT completion for first recurrence, Karnofsky Performance Status (KPS) at initial diagnosis, total dose and number of fractions at first recurrence, date of initial therapy, status and dates of first and second local recurrences, status of death, and date of death or last follow-up if alive. Median second recurrence free and overall survival times were calculated using the Kaplan-Meier method.

**Results:** All patients had recurrences after initial RT. Overall median survival was 8.3 months, which is comparable to previously published data. In patients over 60 years old, the median overall survival in months was 8.3 versus 6.1 for those <60 years old. Patients with a KPS >70 at initial diagnosis had a median survival of 8.3 months versus 6.0 months in patients with a KPS <70. Doses > 2800 cGy tend to only survive a median of 6.0 months, compared to 6.1 months for < 2800 cGy. Median survival time to second recurrence was 1.9 months for all patients. Median second recurrence survival time for age (>60 vs <60 years) and
total dose of first recurrence (>2800 vs <2800 cGy) were both 1.9 and 3.4 months, respectively. Patients with a KPS>70 at initial diagnosis had a median survival of 1.8 months, versus 1.3 months in patients with a KPS <70.

Conclusions: Hypofractionated radiation may prolong survival by 6 months following recurrence, but despite radiation, patients continue to recur.

11. What was your role in this project?

Chart review, Data coding, analysis and write up for publication.
Currently, there is no medicinal cure for Alzheimer’s disease, which has led many patients to search for alternative therapies, such as reminiscence therapy. The LifeBook project is a modified form of reminiscence therapy that provides patients a valuable opportunity to create a multimedia scrapbook of their personal narratives of health and illness. In order to standardize the LifeBook experience, we created a LifeBook companion guide that outlines the process and includes 13 questions aimed at determining a patient’s individual beliefs and values. LifeBook allows patients to re-examine old photographs, share favorite recipes and music, and ultimately reflect on their own preferences regarding end of life care. In order to investigate the efficacy of LifeBook as a therapeutic agent, we conducted pilot interviews aimed at developing a standardized yet flexible interview protocol to evaluate quality of life, a highly subjective variable. We ultimately decided to utilize a 13 question quality of life scale in combination with a 3 question qualitative survey. We then added 3 open ended questions regarding whether the finished Lifebook guided patients and caregivers through the difficult task of developing advanced directives for their end of life care. However, during patient interviews, questions still had to be altered for a given patient’s mental and emotional state, especially in patients with later stage disease progression. We are currently still in the process of conducting patient interviews and analyzing data to determine whether LifeBook affected the quality of life in patients suffering from Alzheimer’s disease.
| 11. What was your role in this project? | I helped develop methodology and conduct patient interviews |
Variability of heart rate and respiratory rate in rats, after exposure to chronic intermittent hypoxia.

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Variability of heart rate and respiratory rate in rats, after exposure to chronic intermittent hypoxia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Gregory J. Kruper</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Mikkel Fishman</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Thomas E. Dick</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Pulmonary, Neuroscience</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>CWRU</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | A decrease in heart rate variability predicted cardiac pathology (Pincus and Goldberger, Am J Physiol. 266: H1643-H1656, 1994). Further, cardiac arrhythmias were associated with sleep apnea (Mehra et al., Am J Respir Crit Care Med. 173: 910-916, 2006). During sleep apnea, the body experiences periods of intermittent hypoxia. We postulated that intermittent hypoxia alone decreased heart rate variability and that this would be linked with decreased breathing frequency variability due to cardiopulmonary coupling. A secondary hypothesis was whether or not a difference existed between two rodent strains which have very different hypoxic responses.

We implanted wireless pressure transducers to monitor blood pressure in adult male rats (Sprague Dawley/Zivic Miller and Brown Norway/Harlan). Blood pressure was measured before and after conditioning with intermittent hypoxia. Hypoxic exposures consisted of ambient PO2<10% for 15s, followed by 5min of recovery; repeated for 8h per/d for 28d. Respiratory pattern was determined using whole-body, flow-through plethysmography. The animals were allowed to acclimatize to the plethysmographic chamber then exposed to hyperoxia for 5m, then a hypoxic challenge, followed by hyperoxia for 5m and then a hypercapnic challenge followed by hyperoxia.

Linear and non-linear variabilities in the patterns were displayed graphically by Poincaré plots. The pattern of the Poincaré plots was consistent for both two species; greatest variability when the animals were breathing hyperoxia than hypoxia or hypercapnia; both before and after intermittent hypoxic conditioning. However, preliminary results indicate that animals of both species decreased their respiratory variability during...
the baseline hyperoxia after intermittent hypoxic conditioning. In contrast, heart rate variability increased after hypoxic conditioning.

We conclude that the changes in respiratory control appear independent of those in heart rate. Further, decreased variability during hyperoxia without changes in hypoxic and hypercapnic variabilities indicate that the alteration in respiratory control occurred in the network controlling breath-to-breath variability and that the reflex drive dominates the network's intrinsic variability. Finally, present caveats of this study are variability needs to be quantified and sample size needs to be larger.

| 11. What was your role in this project? | Researcher |
The goal of this project is to develop a new class of novel biomimetic nucleobase materials that can coat hydrophobic materials and reduce thrombotic and infectious complications from an implanted device in vivo. 

Peptide Nucleic Acids (PNAs) are novel polynucleobase molecules that can mimic DNA double helices. A major difference between the two is that PNAs have an uncharged peptide backbone compared to a charged phosphoribose backbone in DNA. The only similarities between the two materials are the nucleobases which can follow Chargaff's pairing rules. The DNA nucleobases, Adenine (A), Cytosine (C), Guanine (G), and Thymine (T), can form hydrogen bonds that do not follow Chargaff's rules as well; however, the complementary base pairings G-C and A-T are the more energetically favorable.

We have designed PNA materials that can spontaneously self-assemble on a hydrophobic surface to form a supramolecular polymer. The molecules have three domains - a surface adsorbing hydrocarbon, a single PNA-nucleobase component that mediates certain intermolecular interactions, and a biological component to mediate a specific biological effect. We plan to characterize these model molecules by varying lengths and interaction strengths of each section. Molecular models of the surface assemblies are constructed to explain the molecular and nano-scale phenomena. The final design of the system will use complementary nucleobases to ensure a well-defined surface organization with well-defined positioning of biological components.

If this research is successful, we will be able to ‘program’ the molecular system to surface self-assemble the PNA biomaterials in a specific
manner, enabling more complex surface epitope reconstruction. This could ultimately be used to improve cell adhesion between a hydrophobic biomaterial and endothelial cells, and would reduce thrombotic, infectious, and biocompatibility complications that currently plague patients.

1. Title
   A Novel Self-Assembling Nucleobase Scaffold Coating with Nano-Scale Control

2. Student Presenter:
   Aryavarta M. S. Kumar

3. Co-workers and Collaborators:
   Sona Sivakova, Justin D. Fox, Jennifer E. Green, Stuart J. Rowan, Roger E. Marchant

4. Advisor:
   Roger E. Marchant

5. Departments:
   Biomedical Engineering
   Macromolecular Science and Engineering

6. Institutions:
   Case Western Reserve University

7. Support:
   Funding for this research was provided by the NIH Grant No. NIBIB-EB-001466-01 and by Case MSTP grant T32-GM07250.

8. Please choose your academic program:
   MD PHD

9. What year are you in the program?
   6

10. Body of Abstract (300 words or less)
    Spacing of biological residues is important for biological function. For example, the synergistic peptide sequences RGD and PHSRN in a coating can promote cellular spreading especially when the peptide spacing mimics in vivo distances. Here we propose to design and construct a novel scaffold material to self-assemble on a hydrophobic surface. To allow nano-scale positioning of biological residues, we focused on a supramolecular system composed of small molecular weight monomers. By tuning the distances within the assembly, the scaffold could be used to recreate epitope structures and/or construct arrays of biological residues on a surface with applications ranging from nano-scale microchip technologies to improved biocompatibility of medical devices.

    The model materials in this scaffold design (G-an-G n=12, 18) are a novel nucleobase molecule that have a core hydrocarbon flanked by two peptide nucleic acid connectors with guanines. After adsorbing on a hydrophobic surface, these materials surface self-assemble laterally; all the interactions of the assembly are non-covalent. From molecular modeling, we suggest the guanine moieties form surface hydrogen bonded tape motifs that depend on the local environment and the steric constraints within the assembly. We have used several parameters to tune the molecular assembly at the nano-scale to show that it can potentially be used to synthetically recreate epitope structures on a surface.

    By using the G-a12-G and G-a18-G two monomer system, we can also
phase separate at the nano-scale and, interestingly, the surface concentrations of the two monomers are identical to their solution concentrations even though they have a different number of methylene groups.

If this research is successful, it will generate a novel scaffold material that is tunable that will enable spacing of biological residues to be controlled at the nano-scale.

<p>| 11. What was your role in this project? | Graduate Student |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Linkage Studies of Reading and Spelling Abilities in Children with SSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Iris Kuo</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Lisa Freebairn, Amy Hansen, Dr. Sudha Lyengar, Chris Millard</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Barbara Lewis, Dr. Catherine Stein</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Pediatrics, Department of Epidemiology and Biostatistics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile, NIH</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>

### 10. Body of Abstract (300 words or less)

Speech sound disorders (SSD) are the most prevalent communication disorders in young children. Studies show that both SSD and reading disorders (RD) have a genetic basis. Children with SSD also have a significant chance of developing RD and spelling difficulties.

We have followed the proband (SSD) and family members and assessed their reading and spelling abilities at school age (7-12 yrs). The tests administered include the Woodcock Reading Mastery Test (WR), Wechsler Individual Achievement Test (WIAT), Test of Written Spelling (TW), and Test of Written Language (TOWL). The subtest scores were stepwise adjusted for age, sex, socioeconomic status, and birth order. Linkage analysis of those measures to genetic regions on chromosomes 1, 3, 6, and 15 was performed using Haseman-Elston regression via SIBPAL; these chromosomal regions have been linked to SSD and/or RD in previous studies.

Results show significant linkage (p-value < 0.05) of reading and spelling measures to genetic regions on chromosomes 1, 3, 6 and 15. Chromosome 1 showed linkage to WR Word Identification (1p34.3), TW Total Score and TW Unpredictable Words subtests (1p33), TOWL Thematic Maturity subtest (1p36.11), and the TOWL Contextual Vocabulary and Contextual Style subtests (1p34.4 and 1p33). Chromosome 3 showed linkage to WR Word Attack and Word Identification subtests (3q11.2), TW Total Score and Unpredictable Words subtests (3q13.12), TOWL Contextual Vocabulary and Contextual Style subtests (3p14.1), and TOWL Syntactic Maturity (most significantly linked to 3p12.3 but also 3p14.1). Chromosome 6 was linked to TW Predictable Words (6p21.33). Chromosome 15 showed linkage to WR Word Attack (15q22.1), WR Word Identification (15q21.1), WIAT Listening Comprehension (15q22.1), and TW Unpredictable Words (15q21.1). These findings support the hypothesis that SSD and RD may have a
shared genetic basis, and these chromosomes include genes that influence reading and spelling. Further research is needed to determine more precise genetic locations.

| 11. What was your role in this project? | Analyst |
1. **Title**  
Factors Influencing Prehospital Placement and Utilization of Peripheral Intravenous Catheters

2. **Student Presenter:**  
Kristin Kuzma

3. **Co-workers and Collaborators:**  
Karl Sporer, Glen E Michael, Glen Youngblood

4. **Advisor:**  
Karl Sporer

5. **Departments:**  
Department of Medicine, UCSF and Emergency Medicine at San Francisco General Hospital

6. **Institutions:**  
University of California, San Francisco  
San Francisco General Hospital

7. **Support:**  
None

8. **Please choose your academic program:**  
MD

9. **What year are you in the program?**  
2

10. **Body of Abstract (300 words or less)**  
Study Objective: This study examined the association between IV initiation and utilization rates with paramedic impression, vital signs, skin signs, and Glasgow Coma Score (GCS).

Methods: Electronic records for 34,585 patients transported by ambulance were evaluated for IV placement and utilization. Utilization was defined as a fluid bolus greater than 250 cc or IV medication administration. Basic statistical methods were followed by logistic regression analysis to control for age, race, and gender, paramedic impression, systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), GCS, skin sign color, and capillary refill.

Results: 60% of the patients received IV’s. 70% of the IV’s were not used for treatment. Certain primary impressions had IV’s that were infrequently utilized (n= number in group, % with IV placed, % unused): post seizure (n= 989, 72%, 91%); weakness/dizzy/nausea (n= 3092, 69%, 80%); syncope/near-syncope (n=2034, 81%, 74%); abdominal pain (n=1554, 70%, 86%).

Statistically significant differences were found for paramedic impression, abnormal BP, HR, RR, GCS, and skin signs. 58% of patients with normal vital signs received IV’s, while only 28% of IV’s were utilized for treatment; hypotension 80% received IV (OR=1.211, p=.012) with 70% utilized; hypertension 61% received IV (OR=1.060, p= .027) with 28% utilized; bradycardia 82% received IV (OR=1.588, p<.0001) 51% utilized; tachycardia 66% received IV (OR=1.152, p=.001) 33% utilized; bradypnea 93% received IV (OR=1.638, p=.051) 86% utilized; tachypnea 70% (OR=1.120, p=.024) 33% utilized. 76% of patients with a GCS less than
15 received IV (OR= 1.672, p<.0001) with 32% utilized. The IV initiation rate for abnormal skins was 79% (OR=1.691, p<.0001) with 42% utilized.

Conclusion: Many paramedic impression categories are associated with frequent IV initiation but infrequent utilization. High utilization was associated with hypotension, bradycardia, bradypnea, and abnormal skin signs. Insight into the prehospital patients least likely to require IV utilization could reduce the number of unnecessary IV’s.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. What was your role in this project?</td>
<td>Primary analysis and writing for submission</td>
</tr>
</tbody>
</table>
Complete Endoscopic Closure of Gastric Defects Using a Full-Thickness Tissue Plicating Device

Jessie Lai

Jeffrey Marks, Judy Jin, Christina Williams, Amitabh Chak, Steve Schomisch, Jamie Andrews, Shoichi Okada, Jeffrey Ponsky

Michael McGee

Surgery, Gastroenterology

University Hospitals Case Medical Center, Case Western Reserve University

Natural Orifice Surgery Consortium for Advancement and Research (NOSCAR) 2006 Research Grant Award

MD

2

The current standard of care for closure of hollow visceral defects includes laparotomy or laparoscopy. However, these procedures can lead to incision-related complications, such as wound infections, incisional hernias, and adhesions. A promising alternative to conventional incision-based surgery may be endolumenal closure with natural orifice transluminal endoscopic surgery (NOTES), where surgical access to the peritoneal cavity is gained through a natural orifice and hollow viscera. This eliminates the need for external skin incisions and subsequent complications. This study examined the use of closing standardized gastric defects in a NOTES animal model using a tissue plicating device (TPD), which is currently FDA-approved for endolumenal treatment of gastroesophageal reflux disease. The goal of this study was to evaluate TPD closure for its long-term integrity. Transmural gastric defects were acutely-created in swine (n=10) to simulate perforations, fistulae, or points of NOTES access and then treated with TPD closure. Integrity of the closure was evaluated post-operatively—using upper GI fluoroscopic exams to assess for leakage—and postmortem—using necroscopy to assess for abscess formation or evidence of infection, and closure burst testing to assess for closure strength. There were no complications following the survival transgastric NOTES peritoneoscopy and subsequent TPD closure. Upper gastrointestinal contrast fluoroscopy immediately following closure and on post-operative days 2 and 7 revealed no leakage. On post-operative day 14, necroscopy was performed and revealed a subclinical colonic injury in one animal. Postmortem burst testing revealed that the closure strength was comparable or superior to the strength of native tissue; in 6 of 9 (66%) TPD animals, the bursting occurred in native tissue at a site different from the closure. This study demonstrates that...
endoscopic TPD closure of standardized NOTES gastric defects creates leak-proof, strong closures and supports the need for further examination of TPD closure.

| 11. What was your role in this project? | Student Laboratory Assistant |
### Body of Abstract (300 words or less)

Obscure gastrointestinal bleeding is present in approximately 5% of all patients with gastrointestinal bleeding. Small bowel arteriovenous malformations (AVM) account for 30-40% of obscure GI bleeds. We aimed to characterize the location of AVMs in the small bowel in order to aid decision making in therapeutic approaches towards small bowel AVMs. A retrospective chart review of 658 patients who underwent capsule endoscopy between the 5 year period of May 2002 through July 2007 was performed. 72 patients (39 men, 33 women; mean age of 70, range 42-89) were ultimately diagnosed with small bowel AVM(s) by capsule endoscopy. The location of small bowel AVMs was characterized as proximal, proximal-middle, middle, middle-distal, and distal. The distribution by location of small bowel AVMs was 28 proximal, 11 proximal-middle, 16 middle, 5 middle-distal, and 12 distal. 9 of the diagnosed small bowel AVMs were actively bleeding. The distribution by location of bleeding small bowel AVMs was 5 proximal, 1 proximal-middle, 0 middle, 2 middle distal, and 1 distal. Arteriovenous malformations occurred most frequently in the proximal small bowel, next most frequently in middle small bowel, and least frequently in the distal portion of the small bowel. The advent of balloon enteroscopy allows for an advanced therapeutic endoscopy approach in the treatment of small bowel AVMs. In the era of double and single balloon enteroscopy, we conclude that an anterograde approach be taken first to treat small bowel AVMs, as opposed to a retrograde approach.
| 11. What was your role in this project? |Compiled and analyzed all data from chart review. Wrote IRB proposal, paper and abstract. |
**1. Title**
Does the addition of a full-access under-body blanket to routine thermal care improve heat transfer in cardiac surgery patients?

**2. Student Presenter:**
Geoffrey Langham

**3. Co-workers and Collaborators:**
Steven Insler, Mohamed Bakri, Fady Nageeb, Edward Mascha

**4. Advisor:**
Daniel Sessler

**5. Departments:**
Department of Outcomes Research - Division of Anesthesiology

**6. Institutions:**
Cleveland Clinic Foundation, Cleveland OH

**7. Support:**
NIH T35 short-term training grant

**8. Please choose your academic program:**
MD

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**
Introduction.
Hypothermia during cardiac surgery and in the postoperative period has been associated with adverse outcomes. Conventional (over-body) forced-air warming is highly effective. An under-body cover has been developed for use during cardiac surgery, during which anterior surface access is restricted. We tested the hypothesis that combining under-body forced-air warming with standard thermal care improves core temperature and reduces post-bypass temperature drop ("afterdrop") in patients undergoing cardiac surgery.

Methods.
Patients scheduled for routine, non-emergent cardiac surgery at the Cleveland Clinic between April and July 2006 were enrolled. Patients were randomly assigned to either routine thermal management (n=29) or routine management supplemented by the Arizant Model 635 under-body cover (n=27). Routine heat conservation methods were applied in both groups. Core temperature was measured via bladder Foley catheter.

Results.
Morphometric and demographic characteristics in the two groups were similar, as were anesthetic and surgical management and pre-induction core temperatures. Minimum temperature during bypass was 35.3 ± 1.3 in the standard treatment group and 35.5 ± 1.5 in the active-warming group (P=0.67). The only statistically significant temperature difference between the groups was upon leaving surgery. Afterdrop was similar in the routine management and forced-air groups, and did not differ significantly.

Conclusions.
Patients undergoing routine thermal management and normothermic bypass did not become hypothermic. There was only trivial afterdrop. Lack of afterdrop indicates that normothermic bypass was effective at warming
the core and peripheral tissues. Forced-air warming did not increase core temperature by a clinically important amount in our patients. We note that effective heat transfer would have increased core temperature, even in normothermic patients. Forced-air was minimally effective, presumably, because the under-body cover warms much less surface area than a standard over-body forced-air cover.

| 11. What was your role in this project? | clinical research assistant |
### Title
Semilunar granule cells in the dentate gyrus inner molecular layer mediate persistent activity in mossy cells and hilar interneurons following transient synaptic excitation

### Student Presenter:
Phil Larimer

### Co-workers and Collaborators:
Phil Williams

### Advisor:
Ben Strowbridge

### Departments:
Neurosciences

### Institutions:
CWRU School of Medicine

### Support:
T32-AG000271, R01NS033590

### Please choose your academic program:
MD PHD

### What year are you in the program?
5

### Body of Abstract (300 words or less)
Temporal lobe epilepsy (TLE) affects over one million Americans. TLE is normally treated by drugs that cause global changes in brain pharmacology, with many cognitive side effects. More specific treatments are difficult to achieve due to lack of cellular scale targets. Changes in the anatomy and physiology of dentate granule cells are common in both human patients and in animal models of TLE. We investigate the effects of various perforant path stimulus paradigms on dentate granule cells and an excitatory neuron, semilunar granule cells (SGCs), which we have recently discovered near the granule cell layer. Recent work by Stegen et al. in an excitotoxic animal model of epilepsy demonstrates a drastic enrichment of neurons with location and physiological properties of SGCs. We use acute brain slices from normal rats to record from these cells as well as from their downstream targets. Surprisingly, we find that short trains of perforant path stimuli trigger excitation of hilar neurons that can last up to 2 minutes. During this hilar activity the normal inputs onto hilar neurons, dentate granule cells, are inhibited and do not fire action potentials. However, SGCs fire persistently due to intrinsic plateau currents present in these cells. Simultaneous recordings from multiple neurons show that periods of persistent synaptic input do not occur synchronously in hilar neurons, suggesting that specific neural circuits may be recruited with different temporal patterns. Since SGCs monosynaptically excite hilar mossy cells, spiking activity driven by SGC plateau potentials may mediate the hilar persistent activity. SGCs may function in a memory capacity in healthy rats since previous work in prefrontal cortex has shown that persistent activity of neurons there may mediate short-term memory. The apparent enrichment of SGCs in an epilepsy model may represent a substrate for seizure initiation, making...
SGCs a potential target for antiepileptic treatments.

| 11. What was your role in this project? | Experiment planning and execution, data analysis |
An endothelial cell-selective peptide fluorosurfactant polymer on ePTFE

Coby C. Larsen

Faina Kligman, Roger E. Marchant

Kandice Kottke-Marchant

Department of Biomedical Engineering, Department of Clinical Pathology

Case Western Reserve University, Cleveland Clinic Foundation

The authors gratefully acknowledge the financial support provided by NIH Grant 5R01EB002067 and the facilities provided by the Center for Cardiovascular Biomaterials. Graduate training support was provided for C.C.L. from NIH Grant 5T32GM007250 and an American Heart Association predoctoral fellowship.

MD PHD

6

Statement of Purpose: There is a pressing clinical need for suitable small-diameter vascular prostheses to bypass diseased coronary arteries. A major impediment for use of artificial materials has been the lack of interface blood compatibility. The challenge of tissue engineering a biocompatible blood interface of confluent, healthy endothelial cells (ECs) is that the same matrix proteins (e.g. fibronectin, FN) or FN-derived peptides that bind ECs will also bind platelets and initiate thrombosis. Here, we report a novel biomimetic construct engineered for EC-selective adhesion to vascular graft material; this is accomplished by utilizing a cyclic peptide ligand (CRRETAWAC) with specificity and high affinity for EC integrins, but low affinity for platelet integrins. The EC-selective ligand is presented on a fluorosurfactant polymer (FSP) that allows for simple and durable modification of expanded polytetrafluoroethylene (ePTFE), a clinically relevant vascular graft material.

Results: We found that CRRETAWAC peptide has low affinity for platelet binding. IC50 values for CRRETAWAC inhibition of fibrinogen (FG) binding to immobilized alphallb beta3 platelet integrin and platelet aggregation inhibition were significantly higher than for GRGDSP peptide, suggesting that specific CRRETAWAC-platelet interaction is very limited. EC attachment to CRRETAWAC FSP was alpha5 beta1 integrin specific; attachment was also CRRETAWAC peptide specific. ECs attached with high efficiency to the CRRETAWAC FSP and grew as rapidly as ECs on FN. Cells demonstrated shear stability on CRRETAWAC FSP with no significant cell loss after 4 h of 38 dynes/cm² applied shear stress. Cells...
adherent to CRRETAAC FSP demonstrated production of the antithrombotic mediators PGI2 and tPA comparable to ECs on FN. Conclusions: Our results demonstrate successful modification of ePTFE vascular graft material with an EC-selective FSP that promotes specific EC attachment, growth, shear stability, and function. This biomimetic construct has the potential to promote rapid endothelialization without platelet adhesion on small-diameter vascular grafts.

| 11. What was your role in this project? | I designed and carried out experiments and analysis leading to the conclusions found herein. |
| 1. Title | RGD fluorosurfactant polymer modification of ePTFE facilitates endothelial cell adhesion and growth |
| 2. Student Presenter: | Coby Larsen |
| 4. Advisor: | Roger E. Marchant |
| 5. Departments: | Department of Biomedical Engineering |
| 6. Institutions: | Case Western Reserve University |
| 7. Support: | Presenters gratefully acknowledge the financial support provided by NIH grant 5R01EB002067 and the facilities provided by the Center for Cardiovascular Biomaterials. |
| 8. Please choose your academic program: | MD PHD |
| 9. What year are you in the program? | 5 |

10. Body of Abstract (300 words or less) We have synthesized and characterized a novel peptide fluorosurfactant polymer (PFSP) modification that facilitates the adhesion and growth of endothelial cells on ePTFE vascular graft material. This PFSP consists of a poly(vinyl amine) (PVAm) backbone with integrin binding RGD peptides and perfluorocarbon pendant branches for adsorption and stable adhesion to underlying ePTFE. Aqueous PFSP solution was used to modify the surface of fluorocarbon substrates. Following subconfluent seeding, endothelial cell (EC) adhesion and growth on PFSP was assessed by determining cell population at different time points. Spectroscopic results indicated successful synthesis of PFSP. PFSP modification of ePTFE reduced the receding water contact angle measurement from 120° to 6°, indicating successful surface modification. Quantification of cell population demonstrated reduced EC attachment efficiency but increased growth rate on RGD PFSP compared with fibronectin (FN). Five day cell
population on the RGD PFSP surface approached confluence and was significantly greater than on FN surfaces. There was no appreciable cell population on unmodified fluorocarbon and RGE PFSP surfaces for all time points. Our results indicate successful synthesis and surface modification with PFSP; this is an attractive and effective approach to modifying ePTFE to encourage endothelial cell attachment and growth.
Objective: Approximately 70,000 transurethral microwave thermotherapy (TUMT) procedures for the treatment for lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH) were done last year in the U.S., with an average patient age between 65 -70. There is a high prevalence of underlying cardiovascular disease in this patient population. To assess the potential risk TUMT poses to patients, a retrospective quality control study analyzing changes in blood pressure during TUMT treatment for BPH was conducted.

Methods: Vital signs of 185 patients receiving TUMT treatment from 6 different devices at four institutions were analyzed. Maximum change and percent change in systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) were analyzed. Results were stratified by device used.

Results:
Changes in Blood Pressure During TUMT Treatment (n=185)
Change Systolic Blood Pressure Diastolic Blood Pressure Mean Arterial Pressure
>30 mmHg 77 (42%) 29 (16%) 44 (24%)
>50 mmHg 30 (16%) 2 (1%) 8 (4%)
>70 mmHg 10 (5%) 2 (1%) 1 (0.5%)
> 20% 95 (51%) 103 (56%) 91 (49%)
> 30% 55 (30%) 61 (33%) 51 (28%)
Conclusions: TUMT elicits striking increases in blood pressure, although there were differences depending on the treatment modality. Given the older age and high prevalence of stabilized cardiovascular disease in patients undergoing TUMT, these increases may be potentially harmful. These responses to TUMT have been hitherto unrecognized, and the mechanisms responsible remain to be determined. The results of this study suggest blood pressures should be monitored during TUMT procedures and the procedure or anesthesia should be adjusted according to health risks factors.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>A COLLABORATIVE COMMUNITY EFFORT TO STRENGTHEN PEDIATRIC ADHERENCE STRATEGIES TO ANTIRETROVIRAL THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Melissa Latigo</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Arm's Reach Care Program Staff</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Ajay Sethi, Dr. Joy Amulya</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Epidemiology and Biostatistics</td>
</tr>
<tr>
<td></td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Eva Pancoast Fellowship - Case Western Reserve University</td>
</tr>
<tr>
<td></td>
<td>Arnold P. Gold Foundation Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>3</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>HIV-infected children in Zambia represent 7% of the population on antiretroviral therapy (ART). Though efforts are being made to scale up ART in the pediatric population, it is important to monitor adherence levels and provide adherence support to ensure successful responses to therapy. Currently, there is little data reflecting pediatric ART adherence levels in sub-Saharan Africa, including Zambia. In Lusaka Zambia, the Arm’s Reach Care program (ARC), is one of the programs providing treatment to HIV-infected children through a community-based model. However, previous program reports suggest the need for more effective adherence monitoring and support techniques. The purpose of this study was to provide ARC program staff in Zambia with guidelines and other information for strengthening the pediatric adherence strategies employed by the program. The study involved identification of gaps in adherence strategies through interacting with ARC, NGO and government staff and caregivers. Findings indicate a need for increased psychosocial support training, a multifaceted approach to adherence monitoring and improved program linkages with other home-based care programs and local clinics. Based on these findings, the study made jointly agreed upon short-and long-term recommendations to be implemented in the ARC program.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Study Investigator</td>
</tr>
</tbody>
</table>
Nitric oxide (NO) causes smooth muscle relaxation through a cGMP-mediated pathway involving dephosphorylation of myosin by myosin phosphatase (MP). NO, synthesized by various isoforms of nitric oxide synthase (eNOS, iNOS and nNOS), activates soluble guanylyl cyclase (sGC), which converts GTP to cGMP. cGMP-dependent protein kinase (cGKI) activates MP, leading to smooth muscle relaxation. Small arteries and arterioles display greater resistance, and therefore control blood flow. Previous studies have shown that changes in blood flow result in changes in NO/cGMP signaling in small mesenteric arteries.

Conditions of high blood flow (HF) and low blood flow (LF) were created by ligating 2nd order small mesenteric arteries of every other 1st order arteries (MA1) branching off the superior mesenteric artery in a rat model. Vessels were collected 1 day to 28 days after surgery, and RNA isolated and reverse transcribed. These HF and LF vessels were studied with real-time PCR to quantify differences in mRNA expression in the proximal NO/cGMP signaling pathway, specifically of eNOS, iNOS, sGC, and cGMP-specific phosphodiesterase (PDE5).

Under conditions of chronic HF, and to a lesser extent chronic LF, eNOS and iNOS were rapidly induced and returned to near-normal levels over 28 days. The cGMP-degrading enzyme PDE5 was similarly induced, while the receptor for NO, guanylate cyclase, was variably down-regulated. We propose that this system is behaving as a classic signaling system in a disease state. Increased synthesis of the ligand (NO) mediates acute vasodilatation, balanced by subsequent receptor (sGC) down-regulation and de-sensitization (up-regulation of PDE5) in the target tissue. These
results provide a novel mechanism for the dynamic changes in NO signaling, and perhaps nitrate tolerance, in high flow and low flow disease states. This hypothesis will be tested in future functional studies of these vessels, using pharmacological inhibitors or gene deletions to test component of this pathway.

| 11. What was your role in this project? | Student researcher |
Mortality Prediction by Normal Range Creatinine Phosphokinase Cardiac Markers

Lei Lei

John Mafi

Dr. Frank Peacock

Emergency Department

Cleveland Clinic

NIH T35 Grant

MD

2

Background: Serum concentration of the MB fraction of creatinine phosphokinase (CK-MB) exceeding the institutional cut point aid clinicians in diagnosing acute myocardial infarction. However, it is unclear if fluctuations below the institutional cut off point are prognostically significant. Our purpose is to assess whether fluctuating CK-MB values that never exceed the institutional cut off point are associated with adverse cardiac events.

Methods: We performed a post-hoc analysis using the ItrACS registry of emergency department (ED) patients who were suspected to have acute coronary syndrome (ACS). Patients were included if they had two cardiac markers drawn within six hours of ED presentation, and no marker values exceeded the institutional CK-MB cut point. Adverse cardiac events (ACE) were defined as ED revisit or hospital admission within 30 days, a positive stress test, subsequent myocardial infarction, coronary vascularization, or death. Myocardial ischemia risk was estimated using the acute cardiac ischemia–time insensitive prediction instrument (ACI-TIPI) which predicts cardiac ischemia probability using ECG measurements and other factors such as age, gender, and chief complaint.

Results: Of 17,713 patients, 1,311 (7.4%) had two CK-MB assays within six hours of ED presentation. Evaluation using ACI-TIPI showed that decreasing CK-MB values were associated with a lower risk for adverse cardiac events compared to patients with stable CK-MB (mean difference -2.5%, 95CI -5.1% to 0.0%). Patients with increasing CK-MB values were not at an increased risk for ACE compared to patients with stable CK-MB values (mean difference 1.0%, 95CI -3.0% to 5.1). 30 day ACE were lower with a decreasing CK-MB: OR .67; 95% CI .48-.95, and unchanged
for an increasing CK-MB: OR .96; 95% CI .57-1.6.

Conclusions: An increasing CK-MB below the institutionally defined limit of normal is not associated with an elevated risk of cardiac ischemia and 30 day adverse cardiac events.

| 11. What was your role in this project? | I helped in the literature search and writing of this paper that is being submitted for publication. |
## Body of Abstract (300 words or less)

Background: The long-term objective of this project is to examine mechanisms that regulate axon outgrowth and regeneration that can be used to repair Central Nervous System (CNS) damage caused by traumatic injury, stroke, or neurodegenerative diseases. One of the newest mechanisms of CNS repair involves localized protein synthesis in the growth cone of regenerating nerve axons. Although protein synthesis traditionally has been thought to be restricted to the cell body, recent data have shown that the response to certain guidance molecules requires protein synthesis in the growth cone. While it is known that specialized proteins are needed to bind, transport and target mRNA to the growth cone, it is not known how these mRNA/protein complexes are targeted to growth cones. Data from the Malouf lab has shown that the mRNA binding protein, hnRNP-U, is localized to axon growth cones and that hnRNP-U co-immunoprecipitates with ezrin, a well-known scaffolding protein localized to axon growth cones.

Question: The goal of the summer research project is to identify whether the N-terminus of ezrin is responsible for binding to hnRNP-U.

Approach: Co-immunoprecipitation experiments were performed using Flag-tagged ezrin proteins expressed in NIH/3T3 cells. Vectors for the expression of full-length (1-586-FLAG) and the N-terminal region of ezrin (1-311-FLAG) were made by Christy Gray, a MSTP student in the Malouf lab. NIH/3T3 cells were homogenized 48 hours after being transfected using Lipofectamine 2000. Western analysis was performed using a rabbit polyclonal antibody against hnRNP-U to determine if hnRNP-U binding is associated with expression of the N-terminal region of ezrin.

Results: hnRNP-U co-immunoprecipitated with endogenous as well as overexpressed full-length ezrin (1-586-FLAG) and the N-terminal fragment of ezrin (1-311-FLAG), suggesting that hnRNP-U binds to the N-terminus...
of ezrin. Additional experiments will be performed to demonstrate whether or not the C-terminus can also mediate ezrin-hnRNP-U interactions.

| 11. What was your role in this project? | researcher |
**1. Title**
Effect of Diabetes and Propofol on eNOS Activation Mechanisms in the Heart: Role of Akt and Heat Shock Protein 90

**2. Student Presenter:**
Aaron J. Lindsay, B.S.

**3. Co-workers and Collaborators:**
Peter J. Wickley B.S., Derek S. Damron PhD.

**4. Advisor:**
Derek S. Damron PhD.

**5. Departments:**
Center for Anesthesiology Research

**6. Institutions:**
The Cleveland Clinic, Cleveland, OH 44195

**7. Support:**

**8. Please choose your academic program:**
MD

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**

**BACKGROUND:** Diabetes-induced cardiac dysfunction is characterized by a decrease in myocardial performance independent of vascular disease. Our lab has demonstrated that endothelial nitric oxide synthase (eNOS) is up-regulated in diabetic cardiomyocytes but that NO bioavailability is decreased. eNOS can be activated via an Akt-dependent phosphorylation of serine 1177. Heat Shock Protein 90 (HSP-90) is needed to facilitate the interaction of Akt and eNOS. Akt can be activated via phosphorylation of serine 473.

**OBJECTIVE:** To investigate the phosphorylation state of eNOS and Akt in diabetic cardiomyocytes as well as the levels of HSP-90.

**METHODS:** Cardiomyocytes were obtained from normal and streptozotocin (50mg/kg; IP)-induced diabetic rat hearts 24 weeks after injection. Immunoprecipitation reactions for eNOS, followed by Western blot analyses, were performed on whole cell lysates obtained from normal and diabetic rat hearts to assess phosphorylation of eNOS. Western blot analysis was performed on whole cell lysates obtained from normal and diabetic rat hearts to assess the phosphorylation of Akt. Western blot analysis was performed on whole cell lysates obtained from normal and diabetic rat hearts to assess HSP-90 levels.

**RESULTS:** Immunoblot analysis for eNOS showed a decrease in the phosphorylation of serine 1177 in normal cell lysates compared to diabetic. Immunoblot analysis for Akt showed an increase in the phosphorylation of serine 473 in normal cell lysates compared to diabetic. Phosphorylation of serine 473 on Akt was also increased in lysates treated
with propofol compared to lysates not treated with propofol. Immunoblot analysis for HSP-90 showed decreased levels of HSP-90 in diabetic cell lysates compared to normal.

CONCLUSIONS: Diabetic rat hearts were shown to have increased phosphorylation of AKT, decreased phosphorylation of eNOS, and decreased levels of HSP-90. Propofol was shown to increase the phosphorylation of AKT in normal and diabetic rat hearts.
LO, RUBY

1. Title: Parent Roles in Pediatric Obesity Treatment Programs

2. Student Presenter: Ruby Lo

3. Co-workers and Collaborators:

4. Advisor: Dr. Leslie Heinberg

5. Departments: Epidemiology & Biostatistics, Division of Public Health

6. Institutions: Case Western Reserve University, Rainbow Babies and Children's Hospital

7. Support: T35

8. Please choose your academic program: MD MS

9. What year are you in the program? 2

10. Body of Abstract (300 words or less)

The rapid increase in the prevalence of childhood overweight in the past few decades is of concern because of its many comorbidities, such as diabetes and cardiovascular disease. In response to this trend, the Healthy Kids, Healthy Weight Program at Rainbow Babies and Children’s Hospital seeks to provide an early intervention program for obese pediatric patients while collecting clinical data, in hopes of contributing to the research community as well as providing education and support to the broader community.

In my study, I looked at what parental factors were associated with more successful program outcomes. Success was defined as achieving positive dietary and physical activity changes, greater reductions in BMI and meeting specific goals set by the physicians and program staff in collaboration with the patients. Examples of parental factors that were reviewed included parental self-efficacy, socioeconomic status, parent’s perspective, and maternal depression.

Most of the data that was analyzed was collected from questionnaires, including weight and physical activity self-efficacy questionnaires, change assessment scales and family relationship inventories. Measures of program outcomes were in the form of diet and exercise logs, ratings of participant involvement by the program staff, and BMI tracking.

The following correlations were found: There was a negative correlation between parent involvement during the program and the number of participant absences. Factors that predicted patient absences and low attendance included being male, African American, lower family income, maternal depression and lower parental exercise self-efficacy. Factors that predicted achieving stated goals were being female and having a higher family income. Having a father with a lower BMI predicted having more minutes of activity recorded per week.
Healthy Kids, Healthy Weight is still a young program with ongoing enrollment. Hopefully as more data is collected, the factors that predict success in pediatric obesity treatment programs will be elucidated.

| 11. What was your role in this project? | Data Analysis |
**1. Title**  
Proteomic Approach for the Detection of CCSP-2, a Candidate Serum Marker for Colon Neoplasia

**2. Student Presenter:**  
George Lominadze

**3. Co-workers and Collaborators:**  
Kathleen Lundberg, Sanford Markowitz, Mark R. Chance

**4. Advisor:**  
Mark R. Chance

**5. Departments:**  
Case Center for Proteomics, and Ireland Comprehensive Cancer Center

**6. Institutions:**  
Case School of Medicine

**7. Support:**  
Crile Fellowship. American Gastroenterological Association Student Research Fellowship

**8. Please choose your academic program:**  
MD

**9. What year are you in the program?**  
2

**10. Body of Abstract (300 words or less)**  
Cancers of the colon and rectum are the second leading cause of cancer death among adult Americans. At early stages, colon cancer is highly curable. The current “gold standard” for screening is colonoscopy, which is an invasive and uncomfortable test, and only 10% of adults over the age of 50 have ever had a screening colonoscopy. Thus, there is a need for a more comfortable screening test. Recently, Dr. Markowitz’s lab identified Colon Cancer Secreted Protein-2 (CCSP-2) as a highly overexpressed protein in human colon cancer tumors, compared to normal mucosa of the same patients. CCSP-2 can be detected by western blotting as a circulating biomarker in the blood of mice with human colon cancer xenografts. In order to develop a colon cancer screening test, in this study we aimed to establish a method to detect CCSP-2 in the human serum using highly sensitive proteomic technology. As a test sample we used normal human serum spiked with recombinant CCSP-2 (19 picomolar). For sample deconvolution, we employed sequential steps of protein precipitation, chaotrope solubilization, liquid isoelectric focusing (LIEF), and gel electrophoresis followed by protein band trypsin digestion and matrix assisted laser desorption ionization mass spectrometry (MALDI-MS) to detect CCSP-2 peptides. We successfully identified seven peptides from CCSP-2 each of which unambiguously identified the protein. Thus we have taken a first step toward establishment of CCSP-2 as a testable serological marker of colon cancer, which could lead to the development of a comfortable and simple cancer screening blood test.
| **11. What was your role in this project?** | Doing the experiments, preparing samples for IEF and MS and analyzing them |
Title: Identification of Genes Upregulated in Acute Leukemia Cells In Vivo in an Allogeneic Post-Bone Marrow Transplant Immune Environment

Student Presenter: Florence Loo

Co-workers and Collaborators: Johan Jansson, Andrew Campbell, Kris Lambert

Advisor: Craig Mullen

Departments: Pediatric Hematology/Oncology

Institutions: Strong Children's Research Center, University of Rochester

Support: Strong Childrens Research Center

Academic Program: MD

Year in Program: 2

Body of Abstract:

Background/Hypothesis
This work tested the hypothesis that the in vivo acute leukemia cells upregulate genes that enhance leukemia growth after bone marrow transplant (BMT). This subset of upregulated genes may identify gene targets for therapies to decrease the likelihood of leukemia relapse in BMT patients.

Methods
C1498, a spontaneous arising acute leukemia arising from a C57BL/6 mouse, served as the model for this study. C1498 was recovered from the following environments and gene expression profiles were compared.

Environment: Allogeneic Pressure

In vitro tissue culture: -
Syngeneic C57BL/6 mice not undergoing BMT: None
Mice undergoing allogeneic BMT: +
Mice undergoing allogeneic BMT & post-transplant leukemia vaccine therapy: ++

C1498 leukemia cells and bone marrow were harvested after the development of disease symptoms. Leukemia cells were separated from other bone marrow cells and the total RNA was isolated. Gene expression microarray analysis was performed to identify potential biomarkers for therapy. The data were computed using three separate algorithms: GCRMA, RMA, and MAS 5.0. Upregulated genes were defined as genes demonstrating >4 fold greater change compared to the in vitro control sample. To increase confidence, only genes upregulated in all
sample replicates and all three algorithms were considered genes of interest.

Conclusion
115 genes upregulated in vivo were identified. 192 genes upregulated in the allogeneic post-BMT immune environment were identified.
# A Qualitative Assessment of Primary Care Physicians’ Knowledge, Attitudes, and Practices of HIV Testing

## 2. Student Presenter:
Jose S Lozada

## 3. Co-workers and Collaborators:

## 4. Advisor:
Elaine Borawski, PhD

## 5. Departments:
Epidemiology & Biostatistics

## 6. Institutions:
Case Western Reserve University

## 7. Support:
2007 T35 Short-term Research Training Grant  
National Heart, Lung and Blood Institute, National Institutes of Health  
Grant Number HL080981

## 8. Please choose your academic program:
MD

## 9. What year are you in the program?
2

## 10. Body of Abstract (300 words or less)
On September 22, 2006, the Centers for Disease Control and Prevention (CDC) instituted new recommendations on HIV testing in an attempt to diagnose the estimated 25 percent, or 250,000-300,000 HIV-infected individuals who are unaware of their infection and to improve upon the current trend where 40% of individuals who are diagnosed each year go on to develop AIDS within one year of their diagnosis. The recommendations call for routine “opt-out” HIV screening for all persons aged 13 to 64 in health care settings, regardless of risk. In order for these recommendations to effect change, awareness and acceptance by primary care physicians (PCP) is essential, yet there is very little information regarding physician knowledge, attitudes and practices regarding these new guidelines. In order to better understand the themes that might arise within the PCP community, we conducted qualitative interviews with primary care providers practicing in the greater metropolitan area of Cleveland, Ohio to explore some of the sentiments related to these new guidelines. Half of the physicians interviewed were aware of the new recommendations. Of these, most reported reading about the guidelines through email list-serves to which they belong. After informing all interviewees of the new recommendations, most PCPs were in favor. In practice, most physicians still maintain the old testing paradigm of testing patients with “high risk” behaviors. When discussing issues around comfortable, a recurring theme that was raised was the concern that patients may be offended if they recommend a test. When asked about barriers to testing, the most common answer was the required separate consent that is required by law. The results of this qualitative study illustrate some current themes surrounding HIV testing.
that are evident in the day-to-day practice of PCPs.

| 11. What was your role in this project? | Primary Investigator |
### LU, ELAINE

<table>
<thead>
<tr>
<th>Title</th>
<th>Defining the “Community” in Community Consultation for Emergency Research: Findings from the Community VOICES Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Student Presenter:</td>
<td>Elaine Lu</td>
</tr>
<tr>
<td>Co-workers and Collaborators:</td>
<td>Deborah Ragin, Ilene Wilets, Jennifer Holohan, Rosamond Rhodes, Margaret Smirnoff, Gary Winkel, Maggi Rodriguez, Edmund Ricci, Lynne D. Richardson</td>
</tr>
<tr>
<td>Advisor:</td>
<td>Lynne D. Richardson</td>
</tr>
<tr>
<td>Departments:</td>
<td>Department of Emergency Medicine, Division of Bioethics, Nursing, Behavioral &amp; Community Health Sciences</td>
</tr>
<tr>
<td>Institutions:</td>
<td>Mount Sinai School of Medicine</td>
</tr>
<tr>
<td>Support:</td>
<td>NIH</td>
</tr>
<tr>
<td>Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>

**10. Body of Abstract (300 words or less)**

Objective: Federal rules allowing emergency research without informed consent require “community consultation” but do not provide specific guidance for operationalizing “community” for this purpose. The Community VOICES Study explored public attitudes towards exception from consent for emergency research.

Methods: Participants were recruited from residential buildings that took part in the Public Access Defibrillation Trial, answering questions on the definition of community and appropriate methods of community consultation in a 30-minute interview conducted in English or Spanish. Respondents were asked, “How do you define “community?”.

Results: 355 interviews were obtained from a socioeconomically diverse sample that was 66% female; 42.3% White, 29.3% African American, 22.0% Hispanic, and 6.5% other ethnic groups. Community was defined variably as: location, people/demographics, family/friends, interests/activities, professions, similar experiences or religious beliefs. Respondents’ views differed according to race/ethnicity and place of birth. White respondents were significantly more likely to describe their community based on location (p<.01) or interests/activities (p<.01) whereas African Americans were significantly more likely to describe their community as family/friends (p<.001). Other ethnic groups were significantly more likely to define community according to interests/activities (p<.01). Differences in definition of community were found also for foreign vs. U.S. born participants. U.S. born respondents were significantly more likely to describe their communities by interests/activities (p<.01), professions (p<.05) and similar experiences (p<.05) than were foreign born respondents.
Conclusion: Conducting community consultation for emergency research among immigrant and minority groups requires an understanding of their definitions of community. These findings will assist investigators in developing appropriate consultation processes for emergency research.
Members of the Paramyxovirus family include some of the most prevalent and infectious viruses known, such as Measles, Mumps and Parainfluenzaviruses. Their V accessory proteins are important in viral evasion of the innate immune response. Here, using a cell survival assay that identifies both inhibitors and activators of Interferon Regulatory Factor 3 (IRF3) mediated gene induction, we identified select Paramyxoviral V proteins that inhibited double-stranded (ds) RNA-mediated signaling; these are encoded by Mumps virus (MuV), human Parainfluenza virus 2 (hPIV2) and Parainfluenza virus 5 (PIV5), all members of the genus Rubulavirus. We showed that interaction between V and the IRF3/7 kinases, TANK-binding kinase 1 (TBK1)/Inhibitor of kB kinase e (IKKe), was essential for this inhibition. Indeed, V proteins were phosphorylated directly by TBK1/IKKe, and this, intriguingly, resulted in decreased cellular levels of V. These observations indicate that V mimics IRF3 in both its phosphorylation by TBK1/IKKe and subsequent degradation. This is physiologically relevant as a PIV5 mutant encoding a V protein which cannot inhibit IKKe was much more susceptible to the antiviral effects of dsRNA than the wildtype virus. Hence, the interaction between the V accessory proteins and kinases TBK1/IKKe represents a novel point of regulation in the equilibrium between the pathogen virus and the host innate immune system.
| 11. What was your role in this project? | Designed and performed experiments, analyzed data, wrote paper |
**LUO, ALBERT**

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Association of a single nucleotide polymorphism in the LGALS2 gene with myocardial infarction in an American population</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Albert K. Luo</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Vivek Rajagopal, Gong-Qing Shen, Qing Wang</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Eric J. Topol</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Molecular Cardiology, Department of Genetics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>The Cleveland Clinic Foundation, Case Western Reserve University School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>National Heart, Lung, and Blood Institute, National Institutes of Health</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Myocardial infarction (MI) is a leading cause of death in the Western world. Its pathogenesis includes the chronic formation of plaque inside the coronary artery vessel wall and subsequent acute rupture of the plaque complex, implicating a number of inflammation-mediating molecules, including the cytokine lymphotoxin-a (LTA). It has recently been shown in a Japanese population that functional variation in the LGALS2 gene, whose product is galectin-2, a ligand that binds to LTA, is associated with susceptibility to MI. Reproducibility of case-control genetic polymorphism study results is especially crucial given the relative ease of introducing bias into such studies and the heterogeneity of different study populations. Our aim therefore was to attempt to validate this result in a predominantly Caucasian American population. 1230 individuals who have suffered MI and 951 normal control individuals were genotyped for one single nucleotide polymorphism (SNP) in the noncoding region of LGALS2 which was found to be significantly associated with MI. This C?T substitution affects the transcriptional level of galectin-2 in vitro, potentially leading to altered secretion of LTA, which would then affect the degree of inflammation. The pending data will then be analyzed to determine significant association with MI, if any.</td>
</tr>
</tbody>
</table>
1. Title: Urban office-based buprenorphine/naloxone opioid maintenance therapy: outcomes at 18 month follow-up

2. Student Presenter: Adam G. Mace 1

3. Co-workers and Collaborators: Adelman CA1,2, Pagano ME1,3, Merkin BJ1,2, Defranco R1,2, Ionescu RA1

4. Advisor: TV Parran 1,4

5. Departments: 1Case Western Reserve University School of Medicine, Cleveland, OH 2 St. Vincent Charity Hospital, Rosary Hall, University Hospitals Health System, Cleveland, OH 3 Division of Child Psychiatry, Department of Psychiatry, Case Western Reserve University School of Medicine, Cleveland, OH 4 Department of Psychiatry, St. Vincent Charity Hospital, Cleveland, OH

6. Institutions: Case Western Reserve University

7. Support:

8. Please choose your academic program: MD

9. What year are you in the program? 2

10. Body of Abstract (300 words or less): This is a naturalistic, prospective investigation, with an 18 month follow-up, of 176 opioid dependent patients receiving office-based opioid maintenance therapy. This study examines the demographic and patient characteristics that predict long-term outcomes of urban, office-based therapy with buprenorphine/naloxone (bup/nx). Patients were induced and stabilized on buprenorphine, and attended a concurrent 12-step facilitated support program at an urban community hospital. Eighteen months post-induction, 110 (67%) of patients completed a telephone-based interview regarding their current bup/nx usage, substance use, participation in 12-step recovery, employment, and psychosocial well-being. The primary outcome was abstinence from substance use. Secondary outcomes included engagement in 12-step programs, and employment outcomes. Random effect mixed model regression analyses were conducted to allow adjustment for baseline insurance status and medical and legal conditions. At the 18-month follow-up, 77% of the interviewed sample remained on bup/nx. Patients still taking bup/nx were significantly more likely to be abstinent from any substance use (p=.004), involved in 12-step programs (p=.008), and employed (p=.03) at the 18 month follow-up. Insurance status did not differentiate patients who were taking bup/nx (p=.33), and bup/nx benefit to abstinence and 12-step participation was similar for patients with and without insurance. No differences in opioid use complications were found between patients who were and were no longer taking bup/nx with two exceptions: more constipation (p=.04) and lower craving (p=.0001) were reported among
patients still taking bup/nx in comparison to those who had discontinued therapy. In a diverse population of opioid addicted patients, this study suggests that office-based therapy with bup/nx is effective in promoting long-term abstinence, engagement in 12-step programs, and social functioning.

<p>| 11. What was your role in this project? | Literature review, coordinated data analysis, wrote manuscript |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Serum Troponin Fluctuations Below Institutional Cut-Points Predict Higher Risk of Adverse Cardiac Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>John N. Mafi</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Dr. Nolan McMullin, Lei Lei, MS-II</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Frank Peacock</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>The Cleveland Clinic Foundation</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH T35 Grant</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Introduction: Serum troponins (Tn) are powerful diagnostic markers in assessing acute myocardial infarction. The significance of small Tn fluctuations below the institutional cut-point, however, is not well defined. Our purpose was to evaluate the relationship between Tn fluctuations below the institutional cut-point and adverse cardiac events (ACE).

Materials and Methods: We performed a post-hoc analysis of the I*trACS registry which enrolled Emergency Department (ED) patients with suspected acute coronary syndromes (ACS) across the spectrum of risk. We included all patients with two sets of cardiac markers drawn within six hours of presentation, both of which were below the institution’s pre-specified upper limit of normal. Fluctuation was defined as either an increase or decrease in Tn (either I or T) exceeding 15% of the initial value. Adverse cardiac events (ACE) were defined as a positive stress test, myocardial infarction, coronary revascularization, or death within 30 days of presentation. Risk of ischemia was also evaluated by the acute coronary ischemia-time insensitive prediction instrument (ACI-TIPI).

Results: Of 17,713 patient visits, 2,021 had two Tn results within 6 hours of presentation. Compared to having a stable Tn, patients with a decreasing or increasing Tn ischemia risk per ACI-TIPI that was 7.9% (95CI 3.6-12.2) and 9.7% (95% CI 5.2-14.2) higher, respectively. ACE were higher with any Tn fluctuation: OR 2.25; 95% CI 1.42-3.55 for decreasing Tn, and 3.04; 95% CI 1.94-4.75 if increasing.

Conclusions: Small fluctuations in troponin concentration, below the institutionally defined limit of normal, are associated with a significantly increased risk of cardiac ischemia and 30 day adverse cardiac events.
| 11. What was your role in this project? | Co-author |
Background: Studies have demonstrated worse outcomes for females undergoing VAD implantation and heart transplantation when each is considered independently. However, the impact of gender on outcomes of patients BTT with a VAD is ill-defined.

Methods: A retrospective chart review of patients BTT with a VAD (n=214) between 1984 and 2003 was undertaken. Patients were divided into two groups based on gender. Short- and long-term outcomes were compared between females (n=30) and males (n=184).

Results: Baseline demographics between groups were similar although females were less frequently transplanted across 4 or more HLA antigen mismatches (26.7 vs. 50.5 %, p< 0.05), less likely to have a history of cardiac surgery (43.3 vs. 69.6 %, p< 0.05), and more likely to have a PRA >10% (33.3 vs. 13%, p< 0.05). When comparing survival, females had a slightly lower 30-day (86.7 vs. 92.9%, p= 0.348) and 1-year survival (73.3 vs. 83.2%, p= 0.265). Post-transplantation, females were approximately three times more likely to die of infection (13.3 vs. 4.4%, p= 0.176) or organ failure (6.7 vs. 2.2%, p= 0.352). However, females were less likely to die of cardiovascular disease (0 vs. 5.4 %, p< 0.05) or malignancy (0 vs. 3.8%, p< 0.01). They were also less likely to develop post-transplant lymphoproliferative disease (0 vs. 2.2%, p< 0.05) and moderate/severe transplant vasculopathy at 1 (0 vs. 3.3%, p<0.05) and 7 years (0 vs. 3.3%, p<0.05). When comparing bouts of rejection (ISHLT 3A or >) both groups were similar.

Conclusion: The gender-based differences in outcomes illuminated in this study raise questions as to the underlying basis for these differences and...
provide an opportunity for further investigation. A better understanding of the role that gender plays in the clinical course of heart transplant recipients will allow health care professionals to more effectively manage patients and improve outcomes.

| 11. What was your role in this project? | primary author |
The first case of HIV infection in Uganda was reported in 1982. Prevalence soon rose to 30% in urban areas. Since then, prevalence has fallen but an estimated 1.4 million infected persons live in Uganda. There is an urgent need in Uganda to provide a standard of medical care that permits safe administration of complex antiretroviral therapies (ART).

The Joint Clinical Research Center (JCRC) in Kampala, Uganda is an HIV/AIDS research facility developed in 1991 by Makerere University and Ugandan Ministries of Health and Defense. Providing ARTs to approximately 7,000 HIV-infected individuals, JCRC has extensive patient care medical record collections. We propose that a computerized patient record will enhance patient care and enrich JCRC research infrastructure. We also propose that a patient care and research database system used at an academic HIV clinic in Cleveland, Ohio, could be adapted for use at JCRC.

The Patient Care and Research Database is a custom-built SQL application designed at CASE. The relational database is maintained through a Microsoft SQL Software back end and an SP.NET/web browser front end for editing and browsing. Separate tables are maintained for basic patient information, the patient intake questionnaire, allergies, visits, medications, co-morbidities, inter-current illnesses, vaccinations, screens, test results, repository samples, HIV resistance genotype results and phenotype testing. The investigators traveled to JCRC, deployed a customized version of the application and conducted changes in application structure in response to local providers’ and scientists’ input. An interface was created to import existing electronic records, and
record-by-record validation was conducted for data quality. Customized version acceptability was excellent, as assessed by interviews with local providers and directives. Over 17,000 records were included, representing a range of clinical stages and demographics. The database was used to support a successful grant application, led by Dr. Rodriguez, from the President's Emergency Plan for AIDS Relief.
Background: Although endoscopy is safe for procedures requiring moderate sedation, cardiopulmonary complications can occur from transient hypoxia. Identifying subsets of patients at risk for hypoxic episodes, such as those with obstructive sleep apnea (OSA), may help prevent complications of sedation during endoscopy. Studies involving OSA patient endoscopy under moderate sedation are lacking, and further insight is required to investigate susceptibility to hypoxia.

Primary Hypothesis: Patients at high risk (HR) for OSA are more likely to become hypoxemic under moderate sedation during endoscopy than those not at HR. Goal: Compare rates of hypoxemia by risk level for OSA.

Secondary Hypothesis: OSA is underappreciated in patients undergoing endoscopy with moderate sedation. Goal: Determine proportion of patients that is HR for OSA.

If HR patients are more likely to become hypoxemic, more intensive monitoring may be required to prevent sedation-related complications during endoscopy.

Methods: All outpatients scheduled for colonoscopy or EGD were recruited. If inclusion/exclusion criteria were met and consent was obtained, patients completed the Berlin Questionnaire, a tool for identifying risk level for OSA. Procedural data was abstracted from sedation flow sheets.

Results: 90 patients excluded for not meeting study criteria. 192 completed questionnaire (70 HR, 122 low risk (LR)). 181 underwent questionnaire and procedure (67 HR, 114 LR). 13 were hypoxemic and required increased oxygen (6 HR, 7 LR). Patients not started on 2L/min
O2 via NC (12; 2 HR, 10 LR) and patients up-titrated without documented hypoxemia (11; 5 HR, 6 LR) were excluded. Proportion of hypoxemic HR patients to total HR patients was 10.0% (6/60), while hypoxemic LR to total LR was 7.14% (7/98).

Conclusion: Incidence of hypoxemia between LR and HR groups is not statistically significant. Data collection has been extended; further results are pending. Current data suggests no need to adjust sedation patterns in HR OSA patients.

11. What was your role in this project?

Patient Recruitment, Data Collection
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Noninvasive Coronary Angiography with Dual-Source 64-Slice CT: Influence of Reconstruction Technique and Heart Rate on Individual Coronary Segment Image Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Sachin Malik</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Alex Sassani, MD; Stefan Ruehm, MD PhD</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Stefan Ruehm, MD PhD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Radiology, Section of Diagnostic Cardiovascular Imaging</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>University of California, Los Angeles</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD MS</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Background: The introduction of Dual-Source CT (DSCT) scanners has allowed physicians to perform noninvasive CT coronary angiography with higher temporal and spatial resolution than standard 64-slice and 16-slice CT scanners. However, limitations of the temporal resolution still result in the image quality being dependent upon the heart rate of the patient and the image reconstruction interval. To our knowledge no study has evaluated the image quality of the coronary artery segments individually with DSCT.

Purpose: To evaluate the influence of reconstruction intervals and heart rate in DSCT coronary angiography for optimal image quality of individual coronary artery segments.

Materials and Methods: DSCT was performed in 61 patients. Fifteen datasets were reconstructed in 5% increments from 20-90%. The images were analyzed and graded by two blinded readers through consensus reading using scores ranging from 1 (diagnostic, clear delineation of segment) to 4 (non-diagnostic, vessel structures not differentiable). Coronary artery segments were classified according to the guidelines of the American Heart Association (15 segments).

Results: The mean heart rate was 72.8 ± 16.5 (Range: 40-109). Diagnostic image quality (Score 1-2) was found in 90.22% of all segments (720 of 798). For preliminary analysis a cutoff heart rate of 75 bpm was used based on previous literature. At a heart rate of >75 bpm 11 of 15 segments (excluding proximal LAD, middle LAD, 1st diagonal, and 2nd diagonal) showed optimal image quality in the systolic phase between
25-40% of the R-R interval. At all heart rates diagnostic image quality could be achieved in both systole (25-40%) and diastole (65-80%) for 14 of 15 segments (excluding middle RCA).

Conclusions: With DSCT coronary angiography optimal image quality can be achieved for 11 of 15 coronary artery segments at 25-40% of the R-R interval for patients with a heart rate greater than 75 bpm.

| 11. What was your role in this project? | Project design and plan, data collection, data analysis and interpretation, paper writer. |
1. Title
A High-Throughput Tool for the Analysis of the Humoral Immune Response to Chronic Myelogenous Leukemia

2. Student Presenter:
Ovidiu Marina (1,2,3)

3. Co-workers and Collaborators:
Niroshan Ramachandran (4), Melinda Biernacki (3,5), Wandi Zhang (3), Eugenie Hainsworth (4), Catherine J. Wu (3,6)

4. Advisor:
Catherine J. Wu, MD

5. Departments:
1 Case Western Reserve University School of Medicine
2 Division of Aging, Brigham and Women's Hospital
3 Division of Hematologic Malignancies, Dana Farber Cancer Institute
4 Harvard Institute of Proteomics, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School
5 University of Connecticut School of Medicine
6 Departments of Medicine and Pathology, Brigham and Women's Hospital

6. Institutions:

7. Support:
Case School of Medicine Crile Summer Research Fellowship
Case School of Medicine Office of Geriatric Medicine, American Federation for Aging Research (AFAR) program
Brigham and Women's Hospital, Division of Aging, NIH NRSA Grant 1 T35 AG02681-01
National Cancer Institute grant NCI-1 R21 CA 115043-01 (Dr. Catherine J. Wu, MD)

8. Please choose your academic program:
MD

9. What year are you in the program?
2

10. Body of Abstract (300 words or less)
Background: Treatment with donor lymphocyte infusion (DLI) for patients with chronic myelogenous leukemia (CML) provides an example of a clinically effective tumor response, which is associated with the development of potent humoral immunity. In previous studies, we identified over 50 B-cell defined CML-associated antigens from 7 CML DLI responders. At the same time, a novel method for expressing protein onto a glass slide, enabling the testing for multiple antigens in parallel, has been developed.

Hypothesis: A high-throughput screening tool can be developed for CML-associated antigens and reliably used for the measurement of antibody levels in patient sera.

Methods: We cloned target sequences from the previously-characterized
CML-associated antigens into a Gateway GST-fusion protein expression vector. To simultaneously express these antigens for serologic screening, plasmid DNA encoding the antigens of interest was spotted as an array onto a glass slide. GST-fusion proteins were then expressed in situ by in vitro transcription and translation, and locally bound to the slide with anti-GST antibodies. Reactivity against serum antibodies was detected by immunofluorescence. Test sera were derived from patient samples whose pattern of reactivity had been previously characterized using standard ELISA.

Results: 25 DNA sequences, representing 19 previously-identified antigens, were successfully cloned, sequence-verified, and tested for GST expression in array format. Ongoing studies are under way to refine the detection of antibody binding to these antigens while minimizing background noise.

Conclusions: This promising technology is currently undergoing validation. The development of a large-scale array of CML-associated antigens would enable rapid evaluation of the immunogenicity of different CML-directed treatments, including allogeneic transplant, DLI and novel vaccine approaches. Analyses using this tool may provide insight into the breadth and extent of the humoral immune response that develops following effective clinical immunity, and may potentially identify reliable surrogate markers against which immunity consistently develops following immune intervention.
1. Title | A Usability Analysis of a Healthy Behaviors Website
2. Student Presenter: | David Mark
3. Co-workers and Collaborators: | Dr. Susan Flocke
4. Advisor: | Dr. Susan Flocke
5. Departments: | Family Medicine
6. Institutions: | Case Western
7. Support: |
8. Please choose your academic program: | MD MPH
9. What year are you in the program? | 2

10. Body of Abstract (300 words or less) | Background: The internet is a powerful tool for conveying health information. However, the underserved have been shown to have the most difficulty using the internet. Therefore, a health promotion website was designed for maximum accessibility. The purpose of this study was to conduct a usability analysis of the website among a sample of medically underserved patients with a range of internet experience.

Methods: Adult patients seeking care in one of two safety-net family practices were invited to participate in a usability test. A purposeful sampling design was used to ensure representation from both genders, a range of age groups, and different internet experience levels. Usability testing included an interview during which patients performed three tasks using the website. The time and number of clicks needed to complete each task were recorded and compared across internet experience levels. In addition, opinions on the ease of navigation and recommendations for improvement for the website were recorded.

Results: Overall 41 participants completed the interview. The majority of participants found the website easy to use and helpful for healthy behavior information. Overall participants with no or minimal internet experience performed as well as those with medium or high levels of internet experience across the three tasks. There was a trend of those with no internet experience to take longer to complete the tasks, however this was significant ($p = .01$) for only 1 of the three tasks. Additionally, there was no significant difference in the number of unnecessary clicks in completing the three tasks.

Conclusions: It was found that patients from safety-net practices including those with limited internet experience could successfully navigate the
website. Most importantly, this study demonstrated the potential of carefully designed websites to be an effective tool in the primary care setting for communicating health information and supporting healthy behavior changes.

| 11. What was your role in this project? | Created a survey to test the usability of the ARCH website and conducted 41 interviews. |
Background: The negative health impact of tobacco use increases the need for tobacco users to seek medical attention in hospital facilities. Therefore, many existing smokers can be assessed for current smoking status as well as targeted for smoking cessation interventions while they are hospitalized in-patients. However, there are currently no guidelines in place that address the role of healthcare providers in assessing smoking status and offering smoking cessation interventions among hospital in-patients.

Question: Among hospital in-patients in a public inner-city hospital we examined how often smoking status is assessed with hospital in-patients, which healthcare providers are doing the assessment, and if any smoking cessation interventions are being offered.

Methods: 80 hospital in-patients 48 hours post admission from the following services: medicine, trauma, general surgery, family practice, and gynecology were asked about their current smoking status and any past history of smoking tobacco. Active smokers were given the Fagerstrom Test for Nicotine Dependence and a survey that addressed when they started smoking, the number of past quit attempts, their current desire to quit, and if anyone such as a nurse, physician, or counselor approached them regarding their tobacco use and willingness to quit. We then went to the in-patient medical records for all included smokers and non-smokers and assessed which healthcare providers documented the patient's smoking status and their extent of documentation. Then we looked at orders to see if any nicotine replacement therapy had been ordered for in-patients that were currently smoking.
Results/Conclusions: In summary we found that smoking prevalence is high among hospital in-patients (46%), that patients are variably assessed for smoking status, and that patients are not being offered smoking cessation therapy with nicotine replacement therapy.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Leukocyte Activation Effects on Trans-Endothelial Migration in the Blood-Brain Barrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Sunjay Mathur</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Barbara H. Tucky, Xiaolong Li, and Shumei Man</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Richard M. Ransohoff</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Center for Neuroinflammation, Department of Neurosciences</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Lerner Research Institute at Cleveland Clinic</td>
</tr>
<tr>
<td>7. Support:</td>
<td>This research was performed with funding support in part from POI N538667.</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>3</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Leukocyte trans-endothelial migration (TEM) plays an important role in the pathogenesis of multiple sclerosis. Previous studies used an in vitro blood-brain barrier (IVBBB) with shear forces to examine the role that a transfected human brain microvascular endothelial cell (tHBMEC) layer plays in TEM. This study explores the role that activated leukocytes play in TEM across a resting endothelial layer.

To address whether leukocyte activation results in different migration patterns than those patterns found with tHBMEC activation, leukocytes were isolated from fresh whole heparinized blood obtained from healthy, consenting adult volunteers by density centrifugation. Control leukocytes were directly incubated while other leukocytes were activated with 2.5 micrograms/milliliter of ConA, a concentration we showed to cause mid-optimal stimulation. Activated or unactivated leukocytes were collected after 24 hours of incubation and perfused at a concentration of 5x10^5 cells/milliliter at 9 milliliters/hour over a parallel plate flow chamber of unactivated tHBMECs. The twenty minute perfusions were performed at 37°C under the same conditions as prior activated MVEC perfusions, recorded by Qimaging® QICAM on a Dell® Optiplex computer, and processed using Qimaging® QCapture Pro. Videos were analyzed and leukocyte-MVEC interactions were quantified.

Results showed that activated leukocytes demonstrated increased attachment-detachment and attachment-locomotion behavior. This behavior was different from prior studies showing increased attachment-locomotion behavior with unactivated leukocytes perfused over activated tHBMECs. Thus, there are factors expressed by activated leukocytes themselves that play a critical role in modulating TEM. Further studies will investigate which specific combination of factors is required.
for each step of TEM in order to pinpoint therapeutic targets.

| 11. What was your role in this project? | Performance of studies and/or experiments |
Background: Prior studies have had conflicting results regarding the impact on nursing workload on clinically relevant outcomes for hospitalized patients. We are not aware of any data on the impact of physician workload on such outcomes. Our goal was to measure the effect of physician and nursing workload on short-term mortality for critically ill patients in an intensive care unit.

Methods: Retrospective, observational study performed in a 13 bed medical intensive care unit of an urban teaching hospital. We assessed 2,404 admissions from February 2002 to December 2005. The effects of workload variables on intensive care unit mortality was assessed using multivariable logistic regression adjusted for age, gender, insurance status, comorbid conditions, type and severity of acute illness, neurologic function, and the source of intensive care unit admission. Workload variables, calculated for each calendar day or nursing shift, were intensive care unit census, patient to nurse ratio, and the number of ICU admissions. For each workload variable, the workload relative to individual patients was calculated as the average over her/his entire stay in the ICU. Values are reported as Mean ± SD; p-values < .05 were considered significant.

Results: ICU census was 10.0 ±1.9; nurse:patient ratio was 1.7 ±0.2, daily number of intensive care unit admissions was 3.0 ±1.0. None of the three workload variables were significantly related to ICU mortality (p=0.23 to 0.77).

Conclusion: Workload for intensive care unit physicians and nurses, within the range of variation present, did not influence the short-term
mortality rate among critically ill medical patients.

| 11. What was your role in this project? | Study design, data analysis, reporting. |
An effective diagnostic strategy is pivotal to exclude pulmonary embolism (PE) and/or deep venous thrombosis (DVT) in the adult outpatient setting. One approach is the combination of the VIDAS® D-dimer enzyme-linked immunosorbent assay, with a simplified clinical decision rule, the Wells score, which categorizes patients as having a low, medium, or high pre-test probability of PE or DVT. The integration into clinical practice of this laboratory assay and guidelines for its appropriate use was assessed. A retrospective chart review was conducted on adult patients seen in the emergency department (ED) who had a VIDAS® D-dimer assay performed from September 25, 2007 to May 31, 2007. 771 VIDAS D-dimer assays were performed on 752 patients (238 males, 514 females; age 18-97 years). Of the 425 negative D-dimer results (<600 ng/ml FEU), 56 (13.2%) had completed Wells Criteria, 104 (24.5%) were followed up by imaging studies (68 CT, 14 VQ, 33 DUPLX), and 4 patients (0.9%) were positive for thrombus (1 PE, 3 DVT). Of the 346 positive D-dimer results (>600 ng/ml FEU), 29 (8.4%) had completed Wells Criteria, 284 (82.1%) were followed up by imaging studies (192 CT, 64 VQ, 56 DUPLX), and 29 patients (8.4%) were positive for thrombus (19 PE only, 6 DVT only, 4 PE and DVT). In reference to positive imaging, the performance of the VIDAS® D-dimer assay was as follows: 87.9% sensitivity, 28.3% specificity, 10.3% positive predictive value, and 96.2% negative predictive value. These findings demonstrate the clinical utility of using the VIDAS® D-dimer assay to rule out DVT and/or PE in adult outpatients, the high use of imaging studies, and the low use of a simplified clinical decision rule in the diagnostic work up. Furthermore, the results support lowering the laboratory D-dimer reference range from 600 to 550 ng/ml FEU.
| 11. What was your role in this project? | Co-investigator |
Carney complex is an autosomal dominant disorder characterized by cardiac and extracardiac myxomas, spotty skin pigmentation and endocrine tumors. Mutations of the PRKAR1A gene encoding the R1? regulatory subunit of cAMP-dependent protein kinase A (PKA) will cause 65% of Carney complex. The PKA holoenzyme is an inactive tetramer composed of 2 catalytic(Ca) and 2 regulatory subunits(R1?). After cAMP binding, the catalytic subunits become free proteins with enzymatic activity. To study better the role of the stoichiometry of regulatory vs. catalytic subunits in tumor pathogenesis we thought to develop an in vitro model over-expressing regulatory or catalytic subunits. In this study we created an adenovirus containing the catalytic subunit of PKA, PRKACA; mammalian cells infected with this Ca-adenovirus will over-express Ca protein. The adenoviral vector, human adenovirus serotype 5, is rendered replication defective by deletion of the E1 and E3 genes before transfection. Using the Stratagene’s AdEasy XL adenoviral vector system we first cloned the PRKACA cDNA into a p-shuttle vector and then transfected into E. coli BJ5183 cells with the adenoviral plasmid backbone vector, pAdEasy-1. The E. coli BJ5183 cell line has efficient homologous recombination machinery that allows a double-recombination event between the shuttle vector and the adenoviral plasmid during cell electroporation. The recombinant DNA was amplified and digested at the Pac 1 restriction site, exposing its inverted terminal repeats and allowing transfection into AD-293 cells. Once transfected, the AD-293 cells allows E1 complementation in vivo and thus replication of the engineered virus. High titer virus will efficiently infect mammalian cell lines altering the normal regulatory vs. catalytic stoichiometry. This way we will be able to study the changes in the other catalytic and regulatory subunit expression, examine the effects in cell proliferation and apoptosis and elucidate the
molecular mechanisms underlying the tumor formation in Carney complex patients.

| 11. What was your role in this project? | performed experiments and performed homologous recombination to synthesize virus |
## BACKGROUND
Cancer is the second leading cause of death among Americans. Because of this, medical science has focused its efforts to identify high risk populations. Many techniques are available to identify those who are at risk for cancer; one such technique is genetic testing, such as for the BRCA1 and BRCA2 gene. The somatic presence of these altered genes increases the risk of developing breast cancer by 3 to 7 times over the general population. However, to date there is little evidence that BRCA testing results in a decrease in mortality. Although there are prophylactic treatments (1, 2) available for this high risk population, it is unclear whether genetic testing influences the patient's decision to undergo treatment. This study was undertaken to evaluate whether women who test positive for BRCA1/2 mutations undergo risk-reducing oophorectomy or mastectomy at a higher rate than those women that test negative for BRCA 1/2 mutations. METHODS: Female patient, who were seen at the Center for Human Genetics during 1996 to 2006 were abstracted for information on test results, age and prophylactic treatment taken. Three prophylactic treatments were considered: mastectomy, oophorectomy, and tamoxifen. Patients were restricted to 30-70 years of age and will categorized 10 year periods for analysis purposes. Our analysis confidence interval is 95% and the power is 80%. RESULTS: 600 patient records have been abstracted to date. Results are yet to be obtained. We have abstracted the patient charts through 2004 and have moved on to analyzing the individual prophylactic treatment history of the patient. Once this has been accomplished, the information will be organized into a spreadsheet and analyzed. It is our hypothesis that BRCA+ younger women will tend to undergo tamoxifen treatment, BRCA+ menopausal women will tend to undergo mastectomy, BRCA+ women over 60 will tend to not undergo prophylactic treatment and BRCA- women of all ages will tend not to undergo prophylactic treatment. We expect to
see that women who are carriers for BRCA1/2 will undergo prophylactic treatment more commonly than those that are not carriers. We also expect to see that younger women will elect to undergo less surgical treatment while those that are older will undergo more surgical treatments.
| 1. Title | Characterization of Disordered Eating in Young Children |
| 2. Student Presenter: | Sara Lyn Miniaci |
| 3. Co-workers and Collaborators: | Sumayya Holmes, Melissa Santana, Sarah Worely, Zhiyuan Sun |
| 4. Advisor: | Dr. Ellen Rome |
| 5. Departments: | General Pediatrics |
| 6. Institutions: | Cleveland Clinic |
| 7. Support: | Crile Fellowship |
| 8. Please choose your academic program: | MD |
| 9. What year are you in the program? | 2 |
| 10. Body of Abstract (300 words or less) | Background: Eating disorders (EDs) occur in younger children, often with a delay in recognition due to atypical presentation as compared to adolescents or adults. Purpose: This study aims to characterize the presentation of children ages five to thirteen with EDs to enhance clinician’s early recognition of illness. Methods: Electronic medial records of children ages five to thirteen years presenting from August 1, 2000 to September 13, 2007 with EDs were reviewed for demographic information, past medical history, family history, psychological history, and other factors. Results: The mean age for females (12.4 yrs, SD 1.4) was significantly higher (p=0.034) than the mean age for males (11.5 yrs, SD 1.8); 15.5% of the patients were male. The mean BMI at first presentation was 16.2 for females, and 16.9 for males. The time to diagnosis was 16 months for females and 8 months for males (p=0.008). The majority of patients lived with their biologic parents (69.2% SD). Family history was positive for depression in 54%, eating disorders in 45.5%, and substance abuse in 31%. Anxiety was found in 21.7% (85.7% female); obsessive compulsive disorder was seen in 15.5% (80% female); a specific phobia was seen in 10.3% (80% female); depression was found in 28.9% (82.1% female); suicidality was found in 8.3% (100% female); cutting was seen in 6.2% (100% female); body dysmorphia was seen in 12.4% (66.7% female). Sport involvement was reported in 85.9%; 82% participated in exercise. Fifteen children (26.3%) reporting purging at least once (93.3% female). Conclusion: ED in boys under fourteen years may be more prevalent than... |
Children presenting with ED may be at more risk for depression, anxiety, and phobias leading to the chicken and egg question. Delays in diagnosis impact children significantly, as they are more likely to present with lower BMI.

| 11. What was your role in this project? | Data Collection, Data Entry, Review of Statistics |
1. Title
Experimental and theoretical characterization of the voltage distributions generated by deep brain stimulation

2. Student Presenter:
Svjetlana Miocinovic

3. Co-workers and Collaborators:
Scott F. Lempka, Gary S. Russo, Christopher R. Butson, Jerrold L. Vitek, Cameron C. McIntyre

4. Advisor:
Cameron C. McIntyre

5. Departments:
Dept of Biomedical Engineering, CWRU
Dept of Biomedical Engineering, CCF
Dept of Neurosciences, CCF

6. Institutions:
Case Western Reserve University
Cleveland Clinic

7. Support:
NIH (T32 GM07250, R01 NS047388, R01 NS037019)

8. Please choose your academic program:
MD PHD

9. What year are you in the program?
7

10. Body of Abstract (300 words or less)
Deep brain stimulation (DBS) is an established treatment for Parkinson’s disease, although its therapeutic mechanisms of action are not yet fully understood. A substantial obstacle to the scientific study of DBS has been the inability to accurately predict which brain areas are directly affected by the stimulation. Computational models are typically used to estimate voltage fields generated by DBS, but they have not been experimentally validated. The goal of this study was to characterize the spatial and temporal characteristics of voltage distribution generated by DBS electrodes. We recorded voltages around active DBS electrodes in either a saline bath or implanted in the thalamus and STN of a non-human primate. Recordings were made during voltage-controlled and current-controlled stimulation. The experimental findings were compared to volume conductor electric field models of DBS parametrized to match the different recording environments. Three factors substantially affected the experimental and theoretical measurements: 1) voltage drop across the electrode-tissue interface, 2) variations in DBS electrode impedance, and 3) capacitive modulation of the recorded waveform. Our results show that appropriately parameterized electric field models are able to accurately represent voltage distributions generated by DBS.

11. What was your role in this project?
Planning and execution
| 1. Title | Model-designed parameters for selective deep brain stimulation of the subthalamic nucleus |
| 2. Student Presenter: | Svjetlana Miocinovic |
| 4. Advisor: | Cameron C. McIntyre |
| 5. Departments: | Dept of Biomedical Engineering, Dept of Biomedical Engineering, Centre de Recherche, Center for Neurological Restoration |
| 6. Institutions: | Case Western Reserve University, Cleveland, Ohio Cleveland Clinic Foundation, Cleveland, Ohio Université Laval Robert-Giffard, Beauport, Québec, Canada Cleveland Clinic Foundation, Cleveland, Ohio |
| 7. Support: | NIH (T32 GM07250; R01 NS-47388; R01 NS-37019) and IRSC (MOP-5781) |
| 8. Please choose your academic program: | MD PHD |
| 9. What year are you in the program? | 5 |
| 10. Body of Abstract (300 words or less) | Despite the clinical effectiveness of subthalamic nucleus (STN) deep brain stimulation (DBS) in the treatment of Parkinson’s disease, the underlying neuronal response linked to therapeutic benefit remains unclear. Therapeutic DBS electrode contacts are typically positioned in the dorsal STN/fields of Forel (H2)/zona incerta region, making both STN projection neurons and pallidothalamic (GPI) fibers viable candidates as the therapeutic target of the stimulation. We built a comprehensive computational model of DBS to design selective stimulation parameters for activation of either STN projection neurons or GPI fibers of passage. The goal of this model is to provide guidance in experimental studies addressing the therapeutic neural element(s) in STN DBS of parkinsonian macaques. 

Our model of STN DBS consists of three fundamental components: 1) a 3D anatomical model of monkey basal ganglia, 2) a finite element model of the DBS electrode and resulting electric field, and 3) multi-compartment biophysical models of STN projection neurons and GPI fibers of passage. The STN models include a 3D geometry derived from biotin dextran amine labeled STN neurons of a cynomolgus monkey. Fifty STN neurons and 50 GPI fibers were positioned within the 3D anatomical model. The DBS voltage field in the tissue medium was calculated for Itrel II stimulus waveforms with the Fourier finite element method and applied to the neuron models to evaluate their firing response to the stimulation. 

Monopolar, cathodic, 1V, 90us, 136Hz stimulus trains generated varying degrees of selectivity. Electrode contacts deep within the STN...
activated 72% of STN neurons and only 19% of GPI fibers. Stimulation applied in H2 activated 60% of GPI fibers and only 2% of STN neurons. These results suggest that appropriate selection of the stimulating contact can substantially bias activation of either STN neurons or GPI fibers. Given the common location of therapeutic contacts for clinical STN DBS in H2, our results suggest that GPI fibers may represent an important target of the stimulation.
ErbB2/Neu is an orphan receptor of the EGFR tyrosine kinase family. It is overexpressed in 20-30% of human breast cancers and its overexpression correlates with poor patient prognosis and resistance to chemotherapy. To investigate molecular mechanisms of ErbB2-induced tumorigenesis in the breast, transgenic mice that overexpress c-Neu under direction of a mammary gland-specific promoter (MMTV) were used for gene expression profiling. Among the genes differentially regulated in tumors, LMO4, a member of the LIM-only family of transcriptional regulators, is upregulated 5 fold when compared to wild-type glands. This data has been confirmed by RT-PCR, in situ hybridization and western blotting and suggests that LMO4 is a potential ErbB2 transcriptional target in the mammary gland. Supporting this notion, previous studies have revealed that 65% of ErbB2-overexpressing human tumors also overexpress LMO4. In vitro, LMO4 upregulation is associated with lack of expression of differentiation markers in mammary epithelial cells, while its silencing is associated with decreased proliferation, migration and invasion. In transgenic mice, LMO4 overexpression in the mammary gland induces epithelial hyperplasia and tumors. However, the mechanisms by which LMO4 regulates cell proliferation remain unknown. We postulated that LMO4 is required for ErbB2-mediated induction of proliferation. To identify the mechanisms by which LMO4 regulates proliferation of breast cancer cells, we have reduced LMO4 by 85% in ErbB2-dependent breast cancer cells using siRNA. Loss of LMO4 induces a concomitant decrease in Cyclin D1 protein levels by 70%. This reduction in Cyclin D1 expression may involve transcriptional regulation because Cyclin D1 mRNA is also affected by the reduction in LMO4. Current studies are focused on determining if Cyclin D1 mRNA synthesis
is regulated by LMO4. In summary, these data show that maintenance of LMO4 expression is necessary for continued expression of Cyclin D1, a key regulator of mammary epithelial cell proliferation and ErbB2-induced tumorigenesis.
1. **Title**
   Calcitonin-gene related peptide receptor regulation in human heart failure

2. **Student Presenter:**
   Jamin Morrison*

3. **Co-workers and Collaborators:**
   Christine S Moravec¥, W.H. Wilson Tang¥, Jeff Southard€, Lee Southard€, Randall C. Starling¥ and Sathyamangla V. Naga Prasad* 

4. **Advisor:**
   Sathyamangla V. Naga Prasad and Randall C. Starling

5. **Departments:**
   Departments of Molecular Cardiology* and Cardiovascular Medicine¥

6. **Institutions:**
   Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH and €VasoGenix Pharmaceuticals Inc., Lenexa, KS

7. **Support:**
   T35 Short-term Research Training Grant entitled "Research Training in Heart, Lung, Blood & Sleep Disorders," grant number HL082544

8. **Please choose your academic program:**
   MD

9. **What year are you in the program?**
   2

10. **Body of Abstract (300 words or less)**
    Background: Human alpha-Calctonin gene-related peptide (CGRP) is a 37 amino-acid neuropeptide that is a potent vasodilator found widely in the nervous and cardiovascular systems. Studies have shown that CGRP treatment results in strong positive inotropic and chronotropic effects on the heart that is independent of beta-adrenergic receptor (beta-AR) stimulation. CGRP binds to the calcitonin receptor-like receptor (CRLR). The CRLR acts as a CGRP receptor only when it is associated with receptor activity modifying protein-1 (RAMP1). Interestingly, association of CRLR with receptor activity modifying protein-3 (RAMP3) causes CRLR to act as a receptor for adrenomedullin. Adrenomedullin is another neuropeptide found widely throughout the body and is upregulated in human heart failure. Since the presence of CRLR in human hearts has not been previously confirmed nor its regulation elucidated, we wanted to test the levels of CGRP receptor complex expression in human hearts.

    Methods: Cardiac plasma membrane fractions were isolated from non-failing unmatched organ donors without cardiac disease (n=4) and heart failure samples diagnosed with dilated cardiomyopathy (n=6). The plasma membrane fractions were subjected to CGRP radio-ligand binding assay in the absence and presence of receptor agonist, synthetic human alpha-CGRP (VasoGenix Pharmaceuticals Inc., Lenexa, KS).

    Results: Radio-ligand binding shows that there is a significant increase (38%) in the CGRP receptors (CRLR/RAMP1 complex) in conditions of dilated cardiomyopathy compared to the unmatched non-failing controls (15.25 +/- 1.34 versus 11.05 +/- 1.48 fmol/mg protein, p<0.02). To determine the mechanism of upregulation, RT-PCR is being carried out on cardiac RNA isolates from the non-failing and failing heart samples on
CRLR, RAMP1 and RAMP3.
Conclusion: We have demonstrated that CGRP receptors are upregulated in the myocardium of human failing heart. The relative contribution of RAMP1 and RAMP3 will be determined to elucidate the potential mechanisms of CGRP action in human heart failure.

| 11. What was your role in this project? | Summer research student (primary project researcher) |
1. Title | Activin in Cerebral Ischemic Injury and Hypoxia

2. Student Presenter: | Shibani Mukerji(1)

3. Co-workers and Collaborators: | Ekaterina Katsman(1) and Alison Hall(1,2)

4. Advisor: | Alison Hall

5. Departments: | Neuroscience(1)
                  Pharmacology(2)

6. Institutions: | Case Western Reserve University

7. Support: | MSTP training grant and NIH (NS-39316)

8. Please choose your academic program: | MD PHD

9. What year are you in the program? | 4

10. Body of Abstract (300 words or less)

   Stroke is a major health challenge in the United States, accounting for a third of all deaths and resulting in many individuals living with significantly compromised neural functions. Growth factors such as the Transforming Growth Factor beta family member, activin, are attractive potential therapeutics following acute CNS insult. The filament model of middle cerebral artery occlusion (MCAO) was used to study activin involvement after transient focal ischemia in mice. One hour occlusion followed by 24 hours of reperfusion gave rise to reproducible infarct volumes. To begin to understand the temporal characteristics of activin expression, brain samples from adult mice that had a 1 hour occlusion followed by 1 or 24 hours reperfusion were taken for quantitative real-time PCR. Activin mRNA expression increases were detected at 1 hour of reperfusion but not at 24 hours. Western blot analysis reveals that 24 hours after MCAO in mice there is ipsilateral activation of smad 2/3 protein detected. Further, following brief exposure to hypoxia that has recently been identified to confer protection from subsequent focal cerebral injury, rapid activin mRNA increases were observed. Adult mice placed in sealed normobaric chambers were exposed to 11% O2 for 2 hours. Activin mRNA showed increases at 1 hour but not at 4 or 24 hours following hypoxic exposure. In addition, a cell culture model that simulates some aspects of free radical stress following ischemia demonstrated that exogenous activin prevented neuronal death. Cortical cells at 24 hours were pretreated with activin or medium, challenged with hydrogen peroxide (H2O2), and counted at 48 and 72 hours. Activin treatment given prior to H2O2 prevented free radical-induced cell death. These data suggest that endogenous activin is involved in both acute ischemic injury responses and changes with hypoxia, and point to a possible role for activin in providing neuronal protection after injury.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>A Novel Role for Activin on Cell Survival after Adult Experimental Cerebral Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Shibani S. Mukerji</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Alison K. Hall</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Neurosciences</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve Univ., School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>This work was supported by NIH (NS-057883) to SSM, NIH (NS-39316) to AKH, T32 GM07250 to Case MSTP, and School of Graduate Studies at Case Western Reserve University</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>4</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Ischemic stroke is the 3rd leading cause of mortality and the leading cause of adult disability in the United States, leaving many individuals in urgent need of effective therapeutics. One approach for developing novel therapies is to test if endogenous survival factors minimize neuronal damage when added hours after a stroke. Our lab previously demonstrated that a member of the transforming growth factor-beta superfamily, activin is increased 1 hour after a transient middle cerebral artery occlusion in mice, providing evidence that activin is an early endogenous response to stroke. Data obtained from in vitro neuronal cultures show that activin is a survival factor for cortical neurons and acts as a neuroprotectant in a model of oxidative stress. In this study we test if exogenous activin protects neurons against ischemia in vivo. Activin addition 1 hour prior to stroke reduced tissue death providing &quot;proof-of-principle&quot; that activin protects cells after cerebral ischemia. To further study if activin is a candidate therapeutic, exogenous activin was added 7 hours after stroke onset and tissue analyzed at 24 hours. Activin post-treatment reduced ischemic-induced cell death at 24 hours when compared to vehicle control. Cresyl violet staining revealed that activin maintained more neurons in regions most affected by ischemia as well as in cortical areas adjacent to the initial stroke territory. Current studies are designed to test mechanisms for cell survival and functional outcome of activin administration after stroke.</td>
</tr>
<tr>
<td>Question</td>
<td>Answer</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>This is my thesis project and I performed all the work presented</td>
</tr>
</tbody>
</table>
**1. Title**
Regulation of Sphingosine-1-Phosphate Receptor 1 Surface Expression with T cell

**2. Student Presenter:**
Patrick Murphy

**3. Co-workers and Collaborators:**
Nicholas Funderburg

**4. Advisor:**
Michael Lederman

**5. Departments:**
Department of Medicine, Division of Infectious Disease

**6. Institutions:**
Center for AIDS Research, Case Western Reserve University School of Medicine, and university Hospitals of Cleveland

**7. Support:**
T35 NIH grant for Heart, Lung, Blood and Sleep Research Program, Center for AIDS Research

**8. Please choose your academic program:**
MD MA

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**
Sphingosine-1-Phosphate is thought to promote egress of activated lymphocytes from secondary lymphoid organs through interaction with its receptors. We examined the effects of in vitro T cell activation on expression of the S1P1 receptor and on expression of CD69 that may regulate S1P1 surface expression via intracytoplasmic retention.

Peripheral blood mononuclear cells (PBMCs) were cultured in medium or stimulated with Poly I:C (TLR-3 agonist), the mitogenic lectin phytohemagglutinin (PHA), Poly U (TLR-7,8 agonist), Flagellin A (TLR-5 agonist), bacterial lipopolysaccharide (LPS, TLR-4 agonist), or interferon alpha (IFN α). Surface expression of S1P1 and CD69 was monitored by flow cytometry after cultivation in medium. CD8+ T cells had nearly twice the S1P1 density of CD4+ T cells, and naïve T cells and differentiated effector T cells had greater S1P1 densities than central or effector memory cells. Overnight cultivation with Poly I:C, Poly U, IFN α, and PHA (but not Flagellin or LPS) increased expression of CD69 especially among effector T cells that had greater S1P1 densities than central or effector memory cells. Overnight cultivation with Poly I:C, Poly U, IFN α, and PHA (but not Flagellin or LPS) increased expression of CD69 especially among effector memory CD8+ T cells. Along with upregulation of CD69, increased surface expression of S1P1 was observed but after activation with Poly I:C, Poly U or IFN α, surface expression of S1P1 was less in cells that also expressed CD69. After activation with PHA, S1P1 expression was increased comparably among CD69+ and CD69- populations. Thus T cell activation after exposure to certain TLR agonists and to IFN α results in increased expression of S1P1 on effector memory CD8+ T cells and this increase is attenuated among cells also activated to express CD69, an attenuation not seen after exposure to the T cell mitogen PHA.

Bystander activation by TLR agonists and by type 1 interferon may promote relative retention of activated effector cells in lymphoid tissues, while differential expression of S1P1 on T cell subpopulations may play a
11. What was your role in this project?

<table>
<thead>
<tr>
<th>Role</th>
<th>Research Associate</th>
</tr>
</thead>
</table>

role in their distribution.
**Title:** Characterization of Atherosclerotic Lesions with Cryoimaging

**Student Presenter:** Mike Nguyen

**Co-workers and Collaborators:** Olivier Salvado, Robert Hoffman

**Advisor:** Jeff Duerk, Jeff Sunshine, Dave Wilson

**Departments:** Radiology, Biomedical Engineering

**Institutions:** Case Western Reserve University

**Support:** NIH T35

**Please choose your academic program:** MD

**What year are you in the program?** 2

**Body of Abstract (300 words or less)**

During the process of atherosclerosis, arteries undergo physiological changes that can be observed both grossly and histologically. The first signs are fatty streaks and as the disease progresses a lumen-narrowing plaque may form. Tissue types that have been identified in these diseased arteries include necrotic core, calcification, lipid, fibrosis, thrombus, hemorrhage, intima, media, and adventitia. Standard histological methods are the gold-standard for classifying tissue types. However, these methods are time-consuming and expensive. We hypothesize that the main tissues in atherosclerotic lesions can be accurately identified using cryoimaging. Cryoimaging is a new imaging modality developed by Professor Wilson where block faces of frozen samples are imaged at high resolution with bright and fluorescent lights. We expect specificity and sensitivity to be tissue type-specific. To test this hypothesis, we designed a double-blind study whereby tissue types of diseased common iliac arteries from human cadavers are identified independently from cryoimages and histological sections. We will perform statistical analysis to compute specificity and sensitivity for the tissues listed above, analyze contingency tables to identify the main sources of errors, and compute the mean and standard deviation of signal intensity for each tissue type. Results are pending.

**Status:**
Common iliac arteries from 11 cadavers have been procured. Brightfield and autofluorescent cryoimages and histological studies have been performed. The next steps are to identify tissue types from the cryoimages and histological sections and then to run statistical analyses.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11. What was your role in this project?</strong></td>
<td>Helped with protocol design, collecting data, and analyzing results.</td>
</tr>
</tbody>
</table>
b-Lactamases are the major mechanism of resistance to b-lactams in Gram negative bacteria. Glu166 is a strictly conserved residue in the omega loop of Ambler Class A b-lactamases and is thought to play an important role during acylation and deacylation of b-lactam antibiotics. Asn170, another conserved amino acid in the omega loop, holds a strategically located water molecule with Glu166 and is also invariant in class A enzymes. Clinical isolates with substitutions at either position have not been found. Our goal was to explore the sequence requirements at Glu166 and Asn170 that are necessary for catalysis in a model class A b-lactamase (SHV-1). Our intention is to understand the essential function of these residues in Class A enzymes.

Using site-saturation mutagenesis we engineered the complete set of amino acid substitutions at positions Glu166 and Asn170. Substitutions at Glu166 and Asn170 result in abolishment of resistance to penicillins, as well as a decrease in resistance to cephaloridine and cephalothin. Surprisingly, some of these variant b-lactamases demonstrated increased resistance to ceftriaxone, ceftazidime, and cefotaxime. This is particularly true of the Glu166Tyr and Asn170Pro mutants. We propose a possible mechanism by which these substitutions confer increased cephalosporin resistance. These amino acid substitutions result in conformational shifts involving the SHV-1 active site, creating a more ideal fit for the larger cephalosporins while decreasing its ability to effectively accommodate and deactivate penicillins. It is hoped that further study, including protein modeling, may elucidate the mechanism for this altered resistance profile.
| 11. What was your role in this project? | Research assistant |
Background-
What is now known as the Mittal Steel Mill in Cleveland is consistently ranked as the largest fixed source of particulate pollutants in the Cleveland area. However, from December 2001 to May 2002, the mill was completely closed. And from June 2001 until May 2004, the mill was operating at half capacity. This change in mill status lends an opportunity to study the health impact of the mill in periods when it is at full capacity and in periods when it is not. This study focused on comparing adverse cardiovascular outcomes in periods of low mill activity versus outcomes in periods of high mill activity.

Methods
Admissions data for all emergency room visits to the main campus of Metrohealth Medical Center in Cleveland with the primary diagnosis (determined by ICD-9 code) was gathered in addition to pollutant data from the three monitoring stations (PM10, PM2.5, O3, SO2, NO, and NO2) with complete data closest to the steel were gathered from March 1999 until March 2007. A total of 13217 total cases were compiled. The cases were further subdivided into 4 groups based on the category of their diagnosis: Angina, Rhythm disorder, Heart Failure, and Myocardial Infarction. The mean number of ER visits was compared for each group for high activity versus low activity months with a wilcoxon nonparametric oneway analysis as well as one a month to month basis to track ER visits directly with pollutant levels with a multivariate analysis.

ER visits were then geocoded to identify all the addresses that fell within a 3 mile radius of the Mill. Records for the close proximity group were then analyzed.

Conclusions-
There were no significant correlations between mill status and number of
ER visits for either the total or the close proximity group. No trend emerged for comparing ER visits with the levels of particular pollutants.

| 11. What was your role in this project? | Investigator |
1. Title | Validation of Acoustic Pharyngometry using Magnetic Resonance Imaging
---|---
2. Student Presenter: | Seong Cheol Oh
3. Co-workers and Collaborators: | Jennifer Frame, Jack Jesberger, Jean Tkach, Ph.D., Susan Redline, M.D., Sanjay R. Patel, M.D.
4. Advisor: | Sanjay R. Patel, M.D.
5. Departments: | Pulmonary/Critical Care and Sleep Medicine
6. Institutions: | University Hospitals Case Medical Center, Case Western Reserve University School of Medicine
7. Support: | Crile Fellowship, NIH HL081385, HL046380
8. Please choose your academic program: | MD
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | Obstructive sleep apnea (OSA) is a common disease affecting 2-4% of middle-aged populations characterized by collapse of the oropharynx during sleep [1]. Thus, oropharyngeal size is an important predictor of apnea status. Acoustic pharyngometry is a technique that delivers sound waves through the mouth and utilizes the echoes from the throat to calculate upper airway dimensions. In this project, we attempted to assess the accuracy of acoustic pharyngometry by comparing results to those obtained from MRI in patients with a wide range of airway dimensions.

Eight subjects (2 men and 6 women, mean age 45 y, mean BMI 33.7 kg/m2) were studied. Pharyngometry was performed while awake in the sitting and supine positions [2]. MRI was performed with the patient awake and supine in a T scanner. Images of 256x256 pixels in the transverse plane with a slice thickness of 5.0 mm were acquired. The cross-sectional areas (CSA) of the oropharynx were measured by superimposing a polygon drawing tool on the images through ImageTool.

Minimum CSA (r=0.68), mean CSA (r=0.61) and oropharyngeal volume (r=0.57) by pharyngometry showed good correlation between seated and supine measurements. However, all 3 measures were significantly smaller when supine (mean differences of 0.37 cm2, 0.79 cm2, 4.49 cm3 respectively). On the other hand, little to no correlation was found between supine pharyngometry and MRI measurements.

These data suggest that there is strong correlation between pharyngometry measured while seated and supine. However, due to a small number of subjects the results are statistically not significant. In addition, there was a substantial decrease in airway dimensions while supine, which helps explain why OSA is most severe in this position. The lack of correlation between pharyngometry and MRI measurements is
surprising and suggests further research and refinement of our MRI algorithm is needed.

References:

11. What was your role in this project?

My main role in the project was to analyze the MRI data. I also assisted with recruiting patients and learned about the clinical aspects of sleep apnea by spending time at the pulmonary clinic in University Hospitals.
| 1. Title | Mutations in cardiac ion channels resulting in Brugada Syndrome can be rescued using a common sodium channel polymorphism. |
| 2. Student Presenter: | Sophia M. Onwuzulike |
| 3. Co-workers and Collaborators: | |
| 4. Advisor: | Haiyan Liu |
| 5. Departments: | Heart and Vascular Center |
| 6. Institutions: | MetroHealth System |
| 7. Support: | This work was supported by a Scientist Development Grant from the American Heart Association National Center |
| 8. Please choose your academic program: | MD |
| 9. What year are you in the program? | 2 |
| 10. Body of Abstract (300 words or less) | Mutations in the gene encoding the cardiac sodium channel, SCN5A, can lead to a variety of inherited cardiac diseases that can cause life threatening arrhythmias and sudden cardiac death. One such condition, Brugada Syndrome, characterized by ST-segment elevation in the right precordial leads is an autosomal dominant disease with variable penetrance. It was previously reported that the R282H Brugada Syndrome sodium channel mutation is trafficking deficient. However, co-expression of the common sodium channel polymorphism H558R with the mutation can rescue the function of the mutated channel by restoring trafficking and can explain the incomplete penetrance of the disease. Our hypothesis was that the H558R polymorphism can restore the function of mutated channels through interactions with chaperone proteins. Previous studies have shown that a family of proteins, 14-3-3?, interact with the cardiac sodium channel to alter its function. Therefore, our objective was to determine if the mechanism of rescue is through preferential or altered interaction of the polymorphism with quality control protein chaperones such as 14-3-3. We investigated the mechanism by which the H558R polymorphism affects the sodium channel function and assembly using co-immunoprecipitation. Wild-type sodium channel (hH1) and sodium channel expressing the polymorphism (hH1-H558R) were transfected in HEK 293 cells and co-immunoprecipitation experiments were done using antibody to 14-3-3 to precipitate hH1, or hH1-H558R. Co-IP samples were then analyzed by Western Blot using anti Na+ channel antibody and anti 14-3-3 antibody. Results show that the wild-type hH1 as well as hH1-H558R both precipitate with the 14-3-3 protein confirming the interaction of this chaperone with the cardiac sodium channel. However, both hH1 and hH1-H558R immunoprecipitated with 14-3-3 to similar |
quantitative extent. Therefore we conclude that involvement of 14-3-3 in the specific rescue of the mutated protein by the polymorphism is unlikely.
**1. Title**
The maculo-ocular reflex of the mouse

**2. Student Presenter:**
Brian S. Oommen

**3. Co-workers and Collaborators:**
Robert A. James

**4. Advisor:**
John S. Stahl

**5. Departments:**
Neurology

**6. Institutions:**
University Hospitals of Cleveland,
Case Western Reserve University School of Medicine

**7. Support:**
Crile

**8. Please choose your academic program:**
MD

**9. What year are you in the program?**
2

**10. Body of Abstract (300 words or less)**

Studying eye movements of the mouse allows investigators to use genetically modified animals to explore links between genes, neural signals, and behavior. While eye movements induced by semicircular canal stimulation have been studied in mice, the maculo-ocular reflexes induced by maintained tilts have not been characterized. We measured the maculo-ocular reflexes of the strain C57BL/6 as well as tottering, a strain exhibiting ataxia due to mutation of the P/Q calcium channel.

**Methods:** Awake mice (4 C57BL/6, 2 tottering) were placed in body orientations spanning 360° about the pitch (nose up or down) and roll (ear up or down) directions. The resting horizontal and vertical angular deviations of one eye were measured using videooculography. Results: In both strains, as the nose was pitched downward, the eye assumed progressively higher and more temporal resting positions. Eye elevation increased linearly as pitch angle varied from -90° to 90°. Beyond this range the eye abruptly returned to a neutral position. Prominent horizontal deviation of the eye was generated by downward pitch but upward pitch had little effect. In response to roll tilts, eye elevation increased linearly with ipsilateral tilt in the range of -90° to 90°, and gradually decreased beyond this range, generating a quasi-sinusoidal curve overall. Averaging over the data gathered at pitch angles from 0° to 90° (nose down), tottering exhibited more temporally and vertically displaced eye positions than C57BL/6 by 7.0° and 9.6°, respectively. Conclusions: The maculo-ocular reflexes of the mouse are similar to those of the rabbit, another afoveate and the one best studied to date. Tottering’s larger horizontal and vertical deviations in response to pitch are consistent with an earlier observation that this strain exhibits greater eye elevation at rest.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11. What was your role in this project?</strong></td>
<td>construct experimental apparatus, conduct experiments, analyze data</td>
</tr>
<tr>
<td>1. Title</td>
<td>Statins Reduce the Production of Amyloid Beta through Inibition of Protein Isoprenylation</td>
</tr>
<tr>
<td>---------</td>
<td>------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Stephen Ostrowski</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Brandy Wilkinson</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Gary Landreth</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Neurosciences</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>AG16740</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>6</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Epidemiological evidence suggests that long term treatment with HMG-CoA reductase inhibitors, or statins, decreases the risk for developing Alzheimer’s Disease (AD). However, many studies suggest that the effects of statins on AD cannot be fully explained by reduction of cholesterol. In addition to their cholesterol lowering effects, statins have pleiotropic actions and act to lower the concentrations of isoprenoid intermediates, such as geranylgeranyl pyrophosphate and farnesyl pyrophosphate, which are required for the function of Rho and Rab family proteins. We investigated the effects of these cholesterol independent effects of statins on amyloid precursoer protein (APP) processing in cell culture. In our cell culture model, treatment with Simvastatin or Lovastatin abolishes the membrane localization of Rho and Rab family proteins without affecting cellular cholesterol levels. We show that this has two main effects on APP metabolism. First, in H4 neuroglioma cells, treatment with statins or Toxin A (which specifically inhibits the function of Rho family proteins) reduces the levels of C terminal fragments of APP, leading to decreased production of amyloid beta. Secondly, in N2a neuroblastoma cells and to a lesser extent in H4 cells, statins cause delayed maturation and accumulation of APP. This effect was not seen when Rho family proteins were inhibited with Toxin A, suggesting that this occurs through inhibiton of Rab-mediated vesicular trafficking. We are investigating the effects that this has on the processing of APP to amyloid beta. In conclusion, we show that statins can inhibit the production of amyloid beta through inhibition of protein isoprenylaton. This represents a potential mechanism by which statins may limit AD pathogenesis.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Primary Researcher</td>
</tr>
<tr>
<td>1. Title</td>
<td>A Comparison of the Cost-Effectiveness of Lumbar Fusion Surgery and Lumber Total Disc Replacement</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Jeremiah Palmer</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Amanda Graves, Jeffrey Lange</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Sigurd Berven, MD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Orthopaedic Surgery</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>University of California, San Francisco</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD MS</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Results of prospective, randomized device studies comparing lumbar total disc replacement (TDR) and lumbar fusion indicate that TDR can produce equivalent or superior clinical results at two years in patients seeking surgical treatment for degenerative disc disease (DDD). While this may signal a change in the standard of care for certain patients with DDD, there has yet to be an analysis of the relative effectiveness in the context of incremental cost, a necessary step in evaluating new technologies in an environment of rising health care costs. A Markov health state model is a powerful tool in decision analysis to estimate the relative costs and benefits of different options and determine which parameters have the greatest impact on cost-effectiveness, even in the absence of long-term data. The aim of this study is to compare the relative costs and utilities of lumbar fusion surgery and TDR by calculating the incremental cost-effectiveness ratio (ICER). An expected-value decision analysis model was constructed using the Markov process modeling technique to simulate the possible clinical course and outcomes of each treatment option: a single-level, instrumented lumbar fusion (L4-L5 or L5-S1) or a single level lumbar TDR (L4-L5 or L5-S1). Data from previous studies comparing the two treatment options was used to estimate the costs and utilities associated with each outcome as well as the probability of moving through each health state. Any values unable to be obtained were estimated by conjectural hypothesis. Sensitivity analyses will be performed to assess the effect of adjusting each of the variables. At this time, results are not available, pending the acquisition of additional data from centers where the device studies were performed. The Markov health state model has been built, which will allow for quick results when data is acquired as well as a template to analyze similar new technologies.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Background research, building decision analysis model, data collection and analysis</td>
</tr>
</tbody>
</table>
**Presence of Activin in Psoriatic Skin**

**Student Presenter:** Priscilla Pang

**Co-workers and Collaborators:** Ekaterina Katsman, Pin Xu

**Advisor:** Alison K Hall

**Departments:** Neuroscience

**Institutions:** Case Western Reserve University, School of Medicine

**Support:** Crile Research Fellowship

**Please choose your academic program:** MD MS

**What year are you in the program?** 2

**Body of Abstract (300 words or less)**

The function of activin has traditionally been associated with neural development. It has also recently been implicated in the neurocutaneous regulation of inflammatory agents. Following an acute injury (excisional wound), local protein levels of activin and nerve growth factor (NGF) increase, and a subsequent rise in calcitonin gene-related peptide (CGRP) and substance P (SP) is seen. However, with chronic inflammation, the role of activin remains unknown. In this study, frozen and sectioned samples of human skin with psoriasis – a benign inflammatory skin disorder – were used as models of chronic inflammation. To elucidate the source of activin, immunohistochemistry (IHC) was used to target the peptide on sectioned slides of psoriatic and normal skin. These were compared with sister slides of their respective samples targeting either proliferating cell nuclear antigen (PCNA, for dividing cells) or CD11b (for macrophages, which are known to induce psoriatic lesions). The occurrence of activin was localized to the basal layers of the epidermis. Staining for PCNA revealed the characteristic increased proliferation of epidermal cells, but did not convincingly correlate with regions of increased activin. Equally disappointing was the fact that the CD11b staining protocol appeared to have been unsuccessful, as even known positive rat controls came out inconclusive. It must be noted that the samples used in this study were over 5 years old, which may likely play a role in the reason for the questionable results. To this end, several new approach need to be taken to help identify the source of activin in chronic inflammation: 1) fresh samples of psoriatic skin need to be obtained, 2) a new CD11b IHC protocol needs to be obtained, and 3) a protocol for staining T-cells – which are responsible for the maintenance of psoriatic plaques – needs to be identified and undertaken.
| 11. What was your role in this project? | Researcher |
The ability to understand and act on health information (a.k.a. health literacy) has recently been positioned as a patient safety issue warranting attention. We examined whether patients could understand and demonstrate the instructions found on the primary container label of common prescription medications. We conducted a cross-sectional study using in-person, cognitive interviews with literacy assessment (Rapid Estimate of Adult Literacy in Medicine, or REALM) at a Federally Qualified Health Center (FQHC) in Chicago, and a primary care clinic located within a public hospital in Shreveport, Louisiana. In all, 297 patients were recruited (n=67 from Chicago site). Correct understanding of instructions for four common prescription medications, using 14 different instructional formats, was determined by blinded panel review of patients’ verbatim responses. Rates of understanding ranged from 64 percent to 93 percent across the labels. Patients reading at the 6th grade level or below (low literacy) were less able to understand label instructions. After controlling for potential confounding demographic, socioeconomic, and health status variables, low (Adjusted Relative Risk 2.18, 95% Confidence Interval 1.29-3.25) and marginal (7th-8th grade; Adjusted Relative Risk 1.87, 95% Confidence Interval 1.15-2.75) health literacy skills were significantly associated with misunderstanding instructions as compared to patients with adequate literacy skills. In a comparison of different formats, patients were better able to comprehend instructions that were 1) explicit to the time of day to be taken, 2) minimized cognitive load through separation of dose, interval, and instruction, and 3) avoided giving numeric information in text (i.e. ‘2 times’ vs. “twice”). While we were unable to investigate adherence practices or adverse events associated with medical error, this research supports an association between limited health literacy with a greater likelihood for misunderstanding prescription medication label
instructions. Physicians and pharmacists should be trained to be specific when instructing patients on regimens. Policies should be enacted to standardize label content.

| 11. What was your role in this project? | data collection |
Background: Arterial intima-media thickness (IMT) has been shown to be an important pre-clinical marker of cardiovascular disease. The progression of IMT through adolescence is of interest since the age at which this thickening first presents, the manner of manifestation, and the underlying hormonal mechanisms have not been established. The purpose of this cohort observational study was to describe the natural history of the IMT of 6 subjects from a larger longitudinal study (n=44) and to see if the initial statistically significant decrease over 1.5 years persisted for up to 4 years.

Methods: Ostensibly healthy adolescent girls from the larger study were recruited for this follow-up. Of the 21 eligible subjects, 6 participated. Participants had measurements of salient background variables. High frequency, B-mode ultrasound was used to measure IMT from 3 planes of the distal right common carotid artery. Analysis was limited to descriptive techniques.

Results: Mean age of the subjects was 16.8 (SD 0.6). Mean BMI was 26.7 (SD 5.5), mean total cholesterol was 144 (SD 19) and mean HDL was 45 (SD 7). Mean systolic BP was 114 (SD 14) and diastolic BP was 64 (SD 5). Mean time since the last visit of the previous study was 26.2 months (SD 2.7), ranging from 23 to 30 months. The mean composite change in IMT from baseline to final visit was -0.03mm, -5.0% (SD 13.8). This finding may be placed within the context of findings from the previous larger study: baseline to 6 months -0.01mm, -1.0% (SD 6.05, p=0.10); baseline to 12 months -0.01mm, -1.5% (SD 7.05, p=0.09); and baseline to 18 months -0.02mm, -4.2% (SD 8.37, p=0.08).
Conclusions: This follow-up study shows that the previous statistically significant results are robust over time and the thickness of the common carotid artery appears to decrease through adolescent development. The data also support the idea that hormonal changes during adolescence have a salutary effect on this aspect of cardiovascular health.

| 11. What was your role in this project? | Interpretation and Organization of data |
To combat tumor recurrence after radiofrequency (RF) ablation, drug-containing polymer implants designed to release chemotherapeutic agents into the ablated region have been developed. However, in vivo studies demonstrated that drug released from implants placed in the center of ablated tumors may not penetrate to risk areas located at the tumor periphery. To design a better treatment strategy, a framework of drug transport and elimination was used to develop a three-dimensional (3-D) finite element method (FEM) model of drug distribution in non-ablated and ablated tumors. Doxorubicin transport parameters established in previous studies were then used with this model to simulate drug transport from implants placed in multiple locations around the periphery of tumors. By varying the extent of ablation, implant drug release profile, the implant placement geometry, a wide variety of possible tumor treatments were designed. For each treatment, drug concentration at each location in the tumor was simulated as a function of time.

Because ablated tumors are most likely to recur at the ablation boundary, treatment quality was determined by evaluating the cumulative drug exposure in the outermost 25% of the ablated tumor volume. The doxorubicin distribution simulations found that using multiple implants strategically placed throughout a tumor can maximize drug exposure in the risk areas where tumors are most likely to recur after treatment, providing considerable advantage over using a single implant. This study establishes the viability of using a 3-D FEM model to simulate intratumoral drug delivery from implants after RF ablation and suggests the possibility
of using a similar tool to customize a treatment for each patient. Future work will emphasize validating this approach in an animal model.

| 11. What was your role in this project? | Doctoral student performing master's project research. |
Smallpox is a highly contagious viral disease that was officially declared eradicated in 1980. There are current concerns about its re-emergence and recent research efforts have been focused on estimating its impact on contemporary populations. In order to understand smallpox transmission patterns we reviewed historical data from outbreaks dating back to 1872. A systematic review was used to identify papers from the National Library of Medicine, Ovid, Index Medicus and reference lists of included publications. Two authors reviewed selected papers for smallpox outbreaks. 97 relevant papers were identified, containing data from 121 outbreaks. The standard mean basic reproductive rate was 5.49 (SD=5.65) secondary cases per index case before intervention, ranging from 0 to 17 secondary cases per index case. This number was found to vary according to the setting of the outbreak, year and geographical location. Results are interpreted by number of cases in the outbreak, case-fatality rate and % of cases that were successfully vaccinated. It was determined that the transmission of smallpox was highest in a general hospital setting before the diagnosis of smallpox (R0=9.32, SD=6.40, Range=1 to 17), outbreaks occurring after 1950 (R0=6.26, SD=6.67, Range=0 to 18) and in outbreaks in developing countries (R0=5.67, SD=6.97, Range=0 to 12). According to the reviewed literature, early diagnosis and implementation of control measures, such as case-isolation and contact vaccination, were the most important factors in controlling the outbreak. Given the current lack of herd immunity and its unanticipated nature, a rapid epidemic rise can be expected in the case of a smallpox outbreak before the implementation of public health interventions and in regions with crowding and inadequate infrastructure.
11. What was your role in this project?

<p>| Graduate researcher |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Assessment of perceived barriers to participation in genetic research by families of young children: Exploration of ethnic differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Erika M. Pritchett Burge</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Susan Redline</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>CWRU School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>T35 HL080981</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Background and Rationale: Asthma is the most common chronic childhood condition, affecting 10% of children. Poor and minority children are disproportionately affected. With growing availability of new classes of asthma medications, it is becoming necessary to include biological analysis in each child’s asthma risk profile. If revolutionary discoveries come from medical research utilizing these analyses, the noted underrepresentation of African Americans and other minorities among research participants will affect the generalizability of research conclusions to these high-risk populations in pediatric asthma.

Question: What are the perceived barriers to research participation, specifically genetic/biorepository collection and use, by families of young children? Is there an ethnic or socioeconomic divide?

Methods: A culturally sensitive and clinically effective questionnaire to identify potential barriers to genetic research participation by minority families of young children will be accomplished through a combination of literature review, medical and bioethics expert input and focus group feedback.

Review and interviews were used to compile a discussion guide. Each of three focus groups will include 6-10 adult primary caregivers of asthmatic children who self-identify as African American, Latino or Caucasian. Participants will also be characterized by socioeconomic status (insurance). Key words and concerns expressed during the focus groups will be used to modify preliminary questionnaire, which will be refined with expert assistance and piloted. The final questionnaire will be given to those who refuse any portion of genetic information collection and future |
use in the Personalized Asthma Care Team study. Data from completed questionnaires will be analyzed to determine if there are statistically significant differences among races or socioeconomic groups.

Results: An extensive literature review was performed, and experts in Bioethics and Health Disparities were interviewed to compile a Focus Group Guide. A protocol was submitted to the UHHS IRB. Due to inability to gain IRB approval in allotted time, recruitment for focus groups was not begun during the summer.

11. What was your role in this project?

Performed literature review, interviews, IRB protocol submission
# TESTING THE STATISTICAL SIGNIFICANCE OF PHENOTYPE CORRELATIONS AMONG MEASURES OF BODY SIZE, WEIGHT GAIN AND OBESITY IN CSS INTERCROSS PROGENY

## 1. Student Presenter:
Arvind Raina

## 3. Co-workers and Collaborators:
J. Nadeau

## 5. Departments:
Dept. of Genetics

## 6. Institutions:
Case Western Reserve University School of Medicine

## 7. Support:
NIH T-35 Stipend

## 8. Please choose your academic program:
MD

## 9. What year are you in the program?
2

## 10. Body of Abstract (300 words or less)
In a previous analysis by Burrage et al., intercross progeny resulting from crosses between twenty mammalian Chromosome Substitution Strains (CSS) and the C57BL/6J parental strain were used to test the effect of chromosome substitutions on the following measures of body size, weight gain and obesity: Initial weight (IW), Midpoint weight (MW), Final Weight (FW), Body Mass Index (BMI), Early Weight Gain (EWG; mean weight gain per day during the first half of the study by Burrage et al.), Weight Gain (WG; mean weight gain per day during the entire study by Burrage et al.), Final Weight Gain (FWG; mean weight gain per day during the second half of the study by Burrage et al.). Burrage et al. culled seven strong trait correlations from calculated pairwise correlations among the seven traits in the CSS intercross progeny from each one of the twenty intercrosses, i.e., correlations that accounted for at least fifty percent of the phenotypic variance between trait-pairs. Burrage et al. inferred eight distinct networks from the correlations, and found strong trait correlations present in the progeny of all twenty intercrosses (i.e., progeny of all twenty intercrosses demonstrated strong correlations between MW-FW; EWG-WG; FWG-FW; FWG-BMI; FW-BMI; FW-WG; BMI-WG). In the present analysis, we sought to test the reliability and robustness of the correlations found in the eight distinct networks. We calculate confidence limits (95% confidence level) for correlation coefficients (r) between each pairwise correlation in each distinct network via the (normally-distributed) Z'-transformation. The confidence limits yield statistically significant limits for the ‘r’ values, and suggest that the correlations are statistically significant.
| 11. What was your role in this project? | Performing the analysis |
### Body of Abstract (300 words or less)

Asthma exacerbations are a significant economic and healthcare burden with known precipitants but relatively undefined risk factors. We propose that characteristics other than severity of airflow obstruction can identify asthmatics who are exacerbation-prone from those who are not. 142 asthmatics were enrolled in a case-control study (61 cases; 81 controls) investigating mechanisms of asthma exacerbation. “Exacerbators,” or cases, were defined by oral prednisone use for asthma within the last 2 years, whereas “non-exacerbators,” or controls, had not experienced an exacerbation requiring prednisone since age 12. Asthmatics on chronic oral prednisone were excluded. Subjects were recruited using community advertising and our research center’s asthma recruitment database. Subjects were characterized during their study visits by history and physical examination, pulmonary function testing, and asthma characterization questionnaires. Diagnosis of asthma was based upon methacholine bronchoprovocation or bronchodilator reversibility. We found that recent “oral prednisone use” among asthmatics did indeed identify cases with distinct phenotypic differences from controls. Health care utilization was significantly greater in cases than controls when evaluated by ER visits, hospitalizations, and intubations (p < 0.05 by chi square for all analyses). Weekly asthma symptoms and albuterol use were greater in cases than controls (p < 0.05 by rank sum). FEV1/FVC was lower in cases (64.4% ± 17.7%) than controls (72.2% ± 12.7%) (p=0.003), but there was no statistically significant difference in FEV1% predicted or PC20. Although there were more women than men in the total cohort, there was no statistically significant difference in gender distribution between cases (66.7% women) and controls (62.3% women). Recruitment of exacerbation-prone asthmatics utilizing “recent oral prednisone use” therefore enables the identification of phenotypically...
distinct asthmatics. This may serve as a useful strategy for the identification of unique exacerbation-prone asthmatics in future studies of mechanisms of asthma exacerbation.

| 11. What was your role in this project? | For this project, I did background literature reviews of the case control study, helped construct the research question, helped define inclusion/exclusion criteria, helped with recruitment, ran study sessions with some of the patients in the case control study and collected data in the form of the questionnaires and pulmonary function tests. I also worked on the final interpretation of this research. |
Angiogenesis, the growth of new blood vessels from pre-existing vessels, is an important physiological process whose regulation is controlled by many factors. Proliferating cancerous cells require an extensive blood supply in order to grow; thus, the regulation of angiogenesis has become an important area of cancer research. Thrombospondin-1 & -2 have been shown to inhibit angiogenesis by binding to the CD36 receptor, which is expressed on the surface of human microvascular endothelial cells (HuMVEC). Preliminary studies performed by the Silverstein lab showed that the activation of protein kinase C (PKC) with a non-physiologic PKC activator (PMA) in human HuMVEC resulted in a decrease in CD36 surface expression and transcription. Further preliminary work pointed to Lysophosphatidic Acid (LPA), a plasma phospholipid, as a possible physiologic regulator of CD36 in HuMVEC.

This project investigated whether LPA regulates CD36 surface expression and transcription in HuMVEC and, if so, if this regulation occurs via PKC activation. CD36 surface expression was quantified using flow cytometry and CD36 transcription was quantified using Real-Time Quantitative PCR. PKC activation was determined by comparing CD36 surface expression and transcription in cells treated with LPA vs. those treated with LPA plus Go 6983, a PKC Inhibitor. Thymeleatoxin, a non-physiologic PKC agonist, was used as a positive control.

We found that LPA decreased CD36 surface expression on HuMVEC in a dose and time-course dependent manner. Treatment with Go 6983 did not appear to have an effect when measured by either flow cytometry or Real-Time PCR, suggesting that either there is a Go 6983/LPA conflict.
or that LPA’s effect on CD36 is not through a PKC-dependent pathway. However, the CD36 expression on all lines of HuMVEC tried was low. Future objectives thus include finding a HuMVEC line which has normal CD36 expression, repeating the experiments, and experimenting with other PKC inhibitors.

| 11. What was your role in this project? | Experiment performance and data interpretation, under the guidance of Jennifer Major. |
| 1. Title | CXCL9 promotes development of IFN-g-producing alloreactive CD8 T cells but is not a dominant factor in directing graft infiltration following heterotopic cardiac allografting |
| 2. Student Presenter: | Joshua M. Rosenblum |
| 3. Co-workers and Collaborators: | |
| 4. Advisor: | Robert L. Fairchild, PhD |
| 5. Departments: | Pathology  
Immunology |
| 6. Institutions: | Case Western Reserve University  
The Cleveland Clinic |
<p>| 7. Support: | Work was supported by RO1 A1 51620 and NIH T32 GM07250. |
| 8. Please choose your academic program: | MD PHD |
| 9. What year are you in the program? | 4 |
| 10. Body of Abstract (300 words or less) | Factors influencing T cell polarization during priming to cardiac allografts are poorly understood. We investigated the role of CXCL9 (MIG) in priming CD8 T cells to allografts and whether MIG recruits primed CD8 T cells to the graft. To measure MIG in the priming site, DCs and B cells were purified from B6 recipients of MHC-mismatched A/J grafts on d 7 post-transplant (pTx), and qRT-PCR was performed. In allograft recipients, DCs produced 50x greater MIG mRNA than B cells. To monitor effector development in the absence of MIG, wt or MIG-/- allografts were performed and purified CD8 T cells were tested by IFN-? ELISPOT on d 7 pTx. For MIG-/- donors, the frequency of IFN-?-producing CD8 T cells was 40% lower than wt allografts. With MIG-/- recipients, the frequency of IFN-?-producing T cells approximates naïve levels. To confirm that this depression of IFN-?-producing effectors is not a result of impaired proliferation, A/J-specific, CFSE-labeled transgenic CD8 T cells were transferred to wt or MIG-/- allograft recipients at the time of transplant. Grafts harvested on d 5 pTx demonstrated no difference in proliferative capacity. To test the role of MIG in graft infiltration, Thy1.1 donor-primed CD8 T cells were transferred to 1) B6 Thy1.2 allograft recipients or 2) MIG-/- B6 Thy1.2 recipients of MIG-/- allografts. Grafts were harvested on d 2 post-transfer and analyzed using FACS. Primed CD8 T cells infiltrate allografts equally regardless of MIG in the graft or recipient. Collectively, these data indicate that APCs produce MIG in the priming site and that MIG promotes development of IFN-?-producing effectors. It appears that MIG is not required to recruit primed T cells to the allograft. |
| 11. What was your role in this project? | I was the primary person responsible for planning and performing experiments. |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Role of the Hox cofactors in the development of spinal motor circuits</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Catherine Rottkamp</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Cynthia L. Wladyka, Katherine J. Lobur, Amy K. Lucky</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Stephen O'Gorman</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Neurosciences</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH RO1 GM056525</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>6</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>It has been demonstrated that differential expression of Hox genes plays an important role in motor pool identity, both rostrocaudally between segments and mediolaterally within segments of the spinal cord. However, the expression pattern of Hox genes by itself is not diverse enough to account for the large number of motor pools. We propose that differential expression of two families of cofactors, the Meis and Pbx proteins, that affect binding affinity and specificity by forming heteromultimers with members of the Hox family, may provide the necessary diversity. We have demonstrated that in general Pbx and Meis factors are widely expressed in ventral spinal neurons. A striking exception exists in the brachial and lumbar expansions where groups of motor neurons fail to express Pbx or Meis. Retrograde transport studies demonstrated that groups lacking expression represent motor pools projecting to specific muscles, while adjacent motor pools express varying combinations of Pbx and Meis proteins. The functional consequences of misexpression of Pbx1 and Meis1 in a normally negative pool were assessed in ovo electroporation into pectoral motor neurons. While misexpressing neurons settled in the pectoral pool, they were less likely to project to the appropriate target. Electromyographic studies showed that motor neurons of overexpressing chicks displayed abnormal spontaneous firing. We have also decided to look at the consequences of lack of Pbx3 function in the adult mouse. This question cannot be addressed in Pbx3 null mice because they die perinatally due to respiratory failure caused by defects in the hindbrain respiratory circuit. We have therefore developed mice with a conditionally null Pbx3 allele. By crossing this mouse with a Hoxb1-Cre line we have eliminated Pbx3 expression in &gt;90% of spinal cord neurons from early stages. These mice are viable into adulthood, but demonstrate gross motor abnormalities including hypokinesia, hind limb</td>
</tr>
</tbody>
</table>
splaying and posturing of the forelimbs and tail. We are in the process of characterizing these mice with the goal of isolating the cause of the motor dysfunction.
**Title**

HIF-1 regulation of Connexin43 in surviving Epicardial Border Zone Myocytes

**Student Presenter:**

Sarah E. Rusk

**Co-workers and Collaborators:**

Juan Carlos Osario

**Advisor:**

Dr. James Coromilas and Dr. Heather S. Duffy

**Departments:**

Department of Pharmacology, Department of Cardiology

**Institutions:**

Columbia University College of Physicians and Surgeons

**Support:**

Dr. Heather S. Duffy’s research is supported with grants from the National Institutes of Health and the American Heart Association.

**Body of Abstract (300 words or less)**

Gap junctions in cardiac tissue provide a continuous path between cells, allowing for low resistance conduction of electrical signals between myocytes. Connexin43 (Cx43) is the most abundant gap junction protein and is primarily found between cardiac myocytes at intercalated disks. Following ischemic events Cx43 is relocalized to the lateral membranes of myocytes. This disrupts electrical coupling of the myocytes, an event known to result in cardiac arrhythmias. Hypoxia inducible factor 1 (HIF-1) is a transcription factor formed by heterodimerization of an alpha and a beta subunit and acts as a mediator of cellular responses to hypoxic conditions. In the presence of oxygen, the HIF-1α subunit is targeted for degradation via prolyl-hydroxylation. Hypoxia stabilizes HIF-1α and allows for heterodimerization of subunits to activate transcriptional regulation. We hypothesized that HIF-1α may be responsible, in part, for regulation of Cx43 in ischemic myocardium. In a canine model of coronary occlusion the LAD was occluded for 3 hours, 48 hours or 5 days and tissue samples taken from surviving epicardial border zone (EBZ) for analysis. Using Western blot analysis we found that LAD occlusion increased HIF-1α and decreased Cx43 in the EBZ as early as 3 hours post-occlusion. Immunofluorescence microscopy showed that lateralization had also begun by that time point. To determine if HIF-1 was directly involved we pharmacologically activated HIF-1 pathway using dimethylxaloylglycine (DMOG), a prolyl-4-hydroxylase inhibitor. Incubation of rat neonatal myocytes with DMOG showed an increase in HIF-1α with concurrent loss of Cx43. To determine if this effect was seen in vivo we infused DMOG into the EBZ via the LAD and found that as levels of HIF-1α increased there was a concurrent loss and remodeling of Cx43. Thus, we conclude that hypoxia alters Cx43 in ischemic myocardium through a HIF-1α
dependent pathway leading to remodeling of Cx43 and associated arrhythmogenesis.

| 11. What was your role in this project? | I assisted Juan Carlos Osario with his research project. I sliced myocardial tissue, carried out Western Blots, and immunostained tissue for examination. I then assisted with data analysis. |
### Body of Abstract (300 words or less)

Cardiac hypertrophy is a common response to a broad range of hemodynamic stress and can be a harbinger of heart failure, a leading cause of morbidity and mortality in the United States. Previous work from our laboratory has identified Kruppel-like factor 15 (KLF15) as a novel negative regulator of cardiac hypertrophy. However, the precise molecular mechanisms by which KLF15 inhibits hypertrophic signaling in the heart remain undiscovered. Given the importance of the Calcineurin-NFAT signaling pathway in the hypertrophic response, we hypothesized that KLF15 may inhibit its effects, in part, via inhibition of this pathway. Here we demonstrate that KLF15 can inhibit Calcineurin-NFAT mediated gene expression and promoter activity. We identify regions within the KLF15 protein that are important for its repressive function. Finally, we show that KLF15 inhibition of target genes is dependent on histone-deacetylase (HDAC) activity. Taken together these data demonstrate that KLF15's anti-hypertrophic effects may be explained via its ability to inhibit Calcineurin-NFAT signaling in the heart.
1. Title | Quantitative trait loci modulating brain amyloid-beta metabolism in a transgenic mouse model of Alzheimer's disease

2. Student Presenter: | Davis Ryman

3. Co-workers and Collaborators: | Yuan Gao, Bruce T. Lamb

4. Advisor: | Bruce T. Lamb

5. Departments: | CWRU School of Medicine, Dept of Genetics  
CWRU School of Medicine, Dept of Neuroscience  
Lerner Research Institute, Dept of Neurosciences

6. Institutions: | Lerner Research Institute, Cleveland Clinic Foundation  
Case Western Reserve University School of Medicine

7. Support: | CWRU MSTP T32 GM07250; NIH Genetics Training Grant T32 GM008613; Glenn/American Federation for Aging Research Scholarship for Research in the Biology of Aging; NIH Grant AG023012; Alzheimer's Association Zenith Award

8. Please choose your academic program: | MD PHD

9. What year are you in the program? | 5

10. Body of Abstract (300 words or less) | Alzheimer’s disease (AD) is characterized by the presence of senile plaques in the brain formed by aggregation of the amyloid beta (Abeta) peptide, a processed product of the amyloid precursor protein (APP). While several genes directly involved in APP processing have been implicated in rare familial AD syndromes, the study of AD patient populations has demonstrated a very significant degree of unexplained heritability for AD risk, resulting from an unknown number of genetic factors which have proven extremely difficult to identify in human studies. Our lab has developed a unique mouse model system for the study of genetic modifiers of AD pathogenesis, by integrating a full genomic copy of R1.40, a mutant allele of APP known to result in familial human AD, into identical integration sites on the genetic background of four different inbred strains of laboratory mice. Intriguingly, mice from the C57BL/6J and DBA2/J genetic backgrounds carrying the R1.40 APP transgene produce identical levels of unprocessed APP, but demonstrate significant, heritable differences in brain Abeta levels. To identify specific loci responsible for the observed genetic control of Abeta metabolism in this model system, we have performed a whole-genome quantitative trait locus (QTL) mapping experiment on a total of 516 animals from a C57BL/6JxDBA/2J intercross, using a dense set of 909 informative SNP genetic markers. Our studies have identified three genetic loci on mouse chromosomes 1, 2, and 7 showing significant or suggestive associations with brain Abeta levels, several of which contain regions syntenic to previous reports of
linkage in human AD.

<p>| 11. What was your role in this project? | lead author |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Thyroid Hormone and its Effects on Reverse Cholesterol Transport in L6 and Clone 9 Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Jose M. Sanchez, MS II</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Faramarz Ismail-Beigi; Bridgette Christopher; and Kim Martin</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td></td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Medicine, Division of Clinical and Molecular Endocrinology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NHLBI Grant Number HL080981, DK61994</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Treatment of rats with thyroid hormone results in a decrease in cardiac cholesterol content even though the biosynthesis of cholesterol in the heart is increased, suggesting that reverse cholesterol transport is stimulated. I investigated whether cholesterol efflux increases in L6 and Clone 9 cells (cells that are responsive to T3).

The rate of cholesterol efflux in L6 cell lines and in a rat liver-derived cell lines (Clone 9) was determined by adding 1 µCi/ml of tritiated-cholesterol to 100% confluent cells for 24h in culture dishes. Cells were pre-treated with 10^-7 M T3 or diluent for 48-72 prior to study. At 24 h, 0.50 mg/ml high density lipoprotein (HDL) or other cholesterol acceptors (0.03% albumin or growth media with 10% fetal calf serum (FCS)) were added to the medium. Samples of 125 µl from the medium were removed at two hour intervals for eight hours for scintillation counting. Cellular protein was also assayed.

In a control experiment, incubation with serum-free media resulted in negligible cholesterol efflux compared to a 15-fold increase in efflux observed using 10% FCS.

Media with 10% FCS yielded the highest cholesterol efflux rates, followed by 0.05 mg/ml HDL and 0.03% albumin. Based on these and dose-response studies, it was concluded that the best acceptors were (in order of preference): 0.50 mg/ml HDL, media with 10% FCS, and 0.05% albumin.

Finally, using either 0.50 mg/ml HDL or media with 10% FCS in cells pre-treated with thyroid hormone, we found no significant difference in
cholesterol efflux rates in cells treated with T3 versus diluent.

We conclude that 1) cholesterol efflux varies based on the cholesterol acceptor in the extracellular environment, 2) Using L6 and Clone 9 cell lines, there is no significant increase in cholesterol efflux by exposure to T3, and 3) We describe an effective method for measuring reverse cholesterol transport in cell lines. Further experiments are required using fresh cardiomyocytes or cardiac cell lines to test the hypothesis.

<p>| 11. What was your role in this project? | Primary Investigator |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>B-cells in Rheumatoid Arthritis and Graves’ Disease show an increased expression of the insulin-like growth factor-1 receptor.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Daniel Sand</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Catherine Hwang, MD, Vibhavari Naik, MD</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Raymond Douglas, MD, PhD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Medicine, Division of Molecular Medicine</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Harbor-University of California Los Angeles Medical Center, and Los Angeles Biomedical Research Institute.</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH Grant EY016339 and Research to Prevent Blindness Unrestricted Grant</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>There is an interaction between Graves’ disease (GD) IgG and the insulin-like growth factor-1 receptor (IGF-1R) on fibroblasts, which induces the expression of the T-cell chemoattractants IL-16 and RANTES. The same holds true for Rheumatoid Arthritis (RA) IgG. Recently we reported an increased population of T-cells of patients with GD expressing the IGF-1R. IGF-1R has also been shown to play a role in T-cell independent B-cell activation, specifically in the activation of B-cells against bacterial polysaccharides. We wanted to determine whether B-cells of patients with GD and RA display IGF-1R differently from control donors. Peripheral blood mononuclear cells were separated from whole blood and stained for flow cytometric analysis on the FACS Calibur machine (BD Biosciences). The staining plan included the IGF-1R as well as positive and negative controls. FCS Express was used for analysis of the data. The data showed a large fraction of B-cells expressing the IGF-1R in patients with GD and RA compared to control. CD19+ B-cells that were IGF-1R+ made up 34.4 +/- 3.99% (mean +/- SE; n=30) of patients with GD compared to 9.5 +/- 2.6% of control (n=24; p&lt;1.5*10^-6). In RA, CD19+ B-cells that were IGF-1R+ made up 20.0 +/- 2.8% (n=19) compared to 9.5 +/- 2.6% of control (n=24; p&lt;0.001). This increase might potentially be a common phenomenon that extends to other autoimmune diseases as well. In addition to GD and RA another example of an autoimmune disease that involves an altered IGF-1R expression is Crohn’s Disease. We will be studying type 1 diabetes mellitus to further investigate this. Additional studies will be helpful in understanding the pathogenesis that underlies those autoimmune diseases and potentially identify therapeutic targets.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Performing experiments.</td>
</tr>
</tbody>
</table>
**Title**: Trauma Patient Urine in the ICU: Is it Dirty?

**Student Presenter**: Mark J. Sando

**Co-workers and Collaborators**: Joseph F. Golob, MD, Jeffrey A. Claridge, MD

**Advisor**: Jeffrey A. Claridge, MD

**Departments**: Department of Surgery: Division of Trauma, Critical Care, Burns, and Life Flight

**Institutions**: MetroHealth Medical Center, Case Western Reserve University

**Support**: National Institute of Child Health and Human Development, Multidisciplinary Clinical Research Career Development Programs Grant K12 RR023264 Fratianne Scholar, Department of Surgery: Division of Trauma, Critical Care, Burns and Metro Life Flight

**Please choose your academic program**: MD

**What year are you in the program?**: 2

**Body of Abstract (300 words or less)**

**BACKGROUND:**
Urinary tract infections (UTIs) are the most common nosocomial infection and create economic burden through increased testing, treatment, and morbidity. The purpose of this study was to define the current practice for obtaining urinalysis (UA) and urine cultures (UCx) in trauma patients admitted to the surgical and trauma intensive care unit (STICU), and to evaluate the association of fever and leukocytosis with UTIs.

**METHODS:**
An 18-month retrospective cohort analysis was performed on consecutive patients admitted for ≥ 2 days to the STICU at a level I trauma center. Data collected included: demographics, injuries, and the first 14 days of daily maximal temperature (TMax), leukocyte count, UA, and UCx. Fever and leukocytosis were defined as Tmax = 38.5°C and leukocyte count = 12,000/mm³, respectively. Positive UA was defined as a positive urine nitrite and/or a positive urine leukocyte (≥ 10/HPF). UTI was defined as a positive UCx (≥ 10⁵ organisms).

**RESULTS:**
510 patients were evaluated for a total of 3839 patient-days. The mean age was 48.6 ± 0.9 and injury severity score was 19.4 ± 0.5. 72% were males and 91% had blunt injuries. 470 UAs and 407 UCx were obtained. 42 (8%) patients had 60 UTIs. Our practice demonstrated a significant association of obtaining UCx with fever and fever + leukocytosis (p < 0.0001), but no association with leukocytosis alone. Our outcomes
revealed no association of UTI with fever, leukocytosis, or fever+leukocytosis. In the patients with a UA and UCx done concomitantly, the sensitivity and specificity was 54% and 80%, respectively for a UA predicting UTI (PPV=35% and NPV=90%).

CONCLUSIONS:
Our practice for obtaining UCx was related to fever and fever+leukocytosis. However, fever and/or leukocytosis were not associated with UTIs in STICU patients. Our study suggests that the paradigm for evaluating UTI needs to be reevaluated in critically ill trauma patients.

11. What was your role in this project?

Data Collection (Chart Review), Data Entry, Analysis, Background Literature Gathering
SCHENK, AUSTIN

<table>
<thead>
<tr>
<th>1. Title</th>
<th>CD8 memory T cells initiate Mig production early post-transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Austin Schenk</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Robert Fairchild</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Pathology &amp; Immunology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case School of Medicine</td>
</tr>
<tr>
<td></td>
<td>Cleveland Clinic Foundation</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH, American Heart Association, CASE MSTP</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>5</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Organ transplantation saves lives but rarely restores a normal life expectancy, in part because many transplanted organs fail prematurely. Transplanted organs are damaged by surgical trauma, oxygen deprivation, reperfusion injury, and immunity. Memory T cells are one type of adaptive immune cell known to participate in graft injury, but mechanisms of memory T cell functioning are incompletely understood. Previously, our laboratory demonstrated in a murine heterotopic cardiac transplantation model that the T cell chemoattractant Mig (CXCL9) is elevated in allogeneic but not syngeneic cardiac allografts at day 3 post-transplant, and that in vitro culture of CD44hi (but not CD44lo) memory phenotype CD8 T cells with allogeneic (but not syngeneic) endothelial cells results in production of the T cell chemoattractant Mig (CXCL9). We now demonstrate in the murine cardiac transplantation model that adoptive transfer of CD44hi memory CD8 T cells elevates the amount of Mig protein detectable in allografts at day 3 post transplant. This allorecognition event was reduced when β2-microglobulin −/− donor grafts were transplanted into allogeneic recipients, and was undetectable when recipient mice lacked CD8 T cells. Administration of antibodies that inhibit IFN-γ and ICOS reduced intragraft Mig levels but antibody inhibition of CD40L or administration of control IgG had no effect. When recipient mice were depleted of neutrophils prior to allogeneic transplantation, intragraft Mig levels were substantially reduced on the third transplant day. We believe that allorecognition of donor MHC I by circulating CD8 memory T cells early post-transplant initiates intragraft Mig production that optimizes subsequent infiltration by effector T cells. The role for neutrophils in this process emphasizes an important aspect of synergism between innate and adaptive immunity.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Dr. Fairchild and I designed the experiments together. I did all of the surgery and benchwork.</td>
</tr>
<tr>
<td>1. Title</td>
<td>Values exemplified by primary care providers</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Stephen Schuldt</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Mary Ruhe; Sharon Weyer</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Kurt Stange</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Family Medicine</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Previous efforts to improve primary care practice may have had limited effect because they attempt to reduce variability without taking into account practice values that motivate behavior. Using a comparative case study analysis of 79 primary care practices in Northeast Ohio, a typology of practice values was created. We identified values that guided primary care practice structure, culture, and provision of care, and observed patterns or values within practices. Primary care values can be classified according to Internal or External focus. We found that Internally focused practices defined their values in relation to their own ability to achieve a desired end while Externally focused practices defined their values in relation to the recipients of their care. Internally focused values included Business focus and Service focus. Externally focused values included Population focus and Patient focus. Further, our analysis suggests predominant practice values often shape practices to the point of minimizing the influence of other values. This was noticed in the absence of Patient focus as an influential value in practices dominated by a Business focus, and by the absence of a Business focus as an influential value in practices dominated by Patient focus. The values typology developed here can be used to understand variation in primary care practices and to tailor practice change strategies by linking to existing motivation. Future research should examine the effect of practice values on patient outcomes and on practice-individualized quality improvement interventions.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Lead author</td>
</tr>
<tr>
<td>1. Title</td>
<td>How Coping Skills Associate with Cardiovascular disease</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Alicia D. Shelly</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Sonja Harris-Haywood, MD MS and Esa Davis, MD MPH</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Family Medicine</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Context: Stress is an emerging risk factor for obesity and coronary heart disease, not being able to cope with stress may contribute to the development of cardiovascular disease (CVD).  

Objective: The purpose of this study was to investigate whether obese/overweight people who are not actively trying to lose weight are more likely to have negative coping skills in comparison to average weight adults. In addition, this study investigates whether adults with negative coping skills have more risk factors for cardiovascular disease.  

Methods: We conducted a cross-sectional study of 200 adults with various weights receiving care at an urban family medicine practice in northeast, Ohio. Data collection consisted of a self-administered questionnaire that assessed demographics, height, weight, health status and coping skills. The “coping skills” items came from two well known scales: Ways of Coping and the COPE questionnaire. The main outcomes were the prevalence of risk factors for cardiovascular disease (CVD) and obese vs. non obese as measured by BMI. A multiple logistic regression was used to assess the relationship of negative coping skills and CVD risk factors and weight. Results: Data is still currently being collected.  

Conclusion: If the results of our study show that obese adults have negative coping skills and that those with negative coping skills are associated with higher prevalence of cardiovascular risk factors; it may suggests that strategies and screening tools needed to address stress and coping are important in weight management programs and early CVD prevention. |
11. What was your role in this project? | I helped develop the project, and took an active role in collecting surveys

1. Title | The Association between Ways of Coping with Stress and Cardiovascular disease Risk Factors

2. Student Presenter: | Alicia Shelly BS

3. Co-workers and Collaborators: | Mia S Bynum, PhD, Sonja Haywood MD

4. Advisor: | Esa M Davis, MD MPH

5. Departments: | Dept. of Family Medicine-Research Division, Case Western Reserve University ; Dept of Psychology, Purdue University

6. Institutions: | Case Western Reserve University, and Purdue University

7. Support: | MD

8. Please choose your academic program: | MD

9. What year are you in the program? | 2

10. Body of Abstract (300 words or less) | Background: Stress plays a role in the risk of cardiovascular disease and obesity. Positive coping strategies help to mediate stress, which may influence health risk behaviors. Whether the types of coping strategies used by adults are associated with increased risk factors for cardiovascular disease and obesity remains unclear.

   Objective: To investigate whether there are differences in the coping strategies across weight categories. To investigate whether there is a difference in the type of coping strategy used by overweight/obese adults that are actively trying to lose weight compared to those that are not trying to lose weight. To investigate whether the type of coping strategy used by adults are associated with risk factors for cardiovascular disease.

   Methods: 251 adults with various BMI's receiving care at two family medicine practices in northeast Ohio completed a self-administered questionnaire that assessed demographics, height, weight, health status and ways of coping. Coping Styles were measured using a combination of the Ways of Coping and the COPE questionnaire. We used logistic regression to examine the relationship of coping styles and risk factors CVD adjusting for confounders.

   Results: All the surveys have been collected; however we are still in the process of analyzing the data.
Conclusion: We hypothesize that the results will indicate that obese adults will tend to use more emotional style coping strategies, than problem-based coping strategies. Also those adults that use emotional style coping strategies will be associated with a higher prevalence of cardiovascular risk factors. These results may suggest that new strategies and screening tools are needed in order to address stress and coping strategies in weight management programs and early cardiovascular disease prevention.
SHENKO, CHRISTINA

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Characteristics of Eligible Non-participants in a Randomized Controlled Trial on Supportive Care in Advanced Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Christina A. Shenko</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Mary Ellen Lawless</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Julia H. Rose, Ph.D.</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Medicine, MHMC; Geriatric Research, Education and Clinical Center, VAMC</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>MetroHealth Medical Center, Louis Stokes VA Medical Center</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Crile Fellowship; NIH grant: NCI-CA10282-01; VHA grant: IIR 03-255 - 1; ACS grant: ROG-04-090-01</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | BACKGROUND: Given recent concerns regarding unequal access to and utilization of novel medical research [1], patient accrual, recruitment and retention in clinical trials have begun to attract more scholarly attention. However, analysis has focused primarily on enrolled participants, and has failed to investigate those who are eligible for enrollment but refuse participation [2,3,4].

METHODS: We analyzed the demographic information from the Aging and Supportive Care in Advanced Cancer (ASC) study, to identify population-level differences between participants (n=335) and non-participants (n=117), who were further stratified as middle-aged (aged 40 to 60) and young-old (aged 61 to 80). We also examined the reasons given by non-participants when asked why they chose not to enroll.

RESULTS: Non-participants were significantly (p<0.05) more likely to be young-old (versus middle-aged), to be living without a partner, and to have a yearly income less than $20,000. There was a trend (p<0.10) of more non-participants being male. Employment status, level of education achieved and self-reported race were not correlated with study participation. Of the 106 non-participants (90.6%) who gave a reason for refusal, 30 (28.3%) felt they did not need the intervention offered, 25 (23.6%) felt the study itself was too burdensome, 17 (16.0%) felt emotionally unable to participate, and the remaining 34 (32.1%) cited various other reasons.

CONCLUSIONS: The finding that non-participants were more likely to be older, to have lower incomes and to have less social support at home is a concern, as this study is testing the efficacy of a coping and communication support for the underserved. Almost a quarter of non-participants cited study demands (e.g., interviews) as their reason for
refusal. Increased knowledge about non-participants in medical research can be useful both to identify those patients unlikely to utilize the intervention and to achieve higher rates of patient accrual in future investigations.

-------------------------------


| 11. What was your role in this project? | I compiled much of the data on non-participants into usable form, and performed the statistical analyses. |
Abstract: Sizemore et al (PNAS, 101(21), 2004) recently identified a subset of ISGs that are not induced in response to interferons (IFNs) in mouse embryonic fibroblast cells (MEFs) doubly null for the expression of I?B kinase a and ß (IKKa and IKKB). Our work has revealed that the IFN-induced transcription of other IKK-dependent ISGs is specifically dependent on IKKB expression. In a microarray experiment, of 584 ISGs induced in a pool of IKKB-/- cells stably restored for IKKB expression, 370 (63%) were not induced in IKKB-/- cells. Several of these genes have been confirmed by Northern and quantitative PCR analysis. We are currently working to identify the mechanism(s) by which IKKbeta is required for the induction of these genes.

This is my graduate thesis project
| 4. Advisor: | George Stark |
| 5. Departments: | Pathology |
| 6. Institutions: | Case School of Medicine, Cleveland Clinic Foundation |
| 7. Support: | NIH |
| 8. Please choose your academic program: | MD PHD |
| 9. What year are you in the program? | 6 |
| 10. Body of Abstract (300 words or less) | Sizemore et al (PNAS, 101(21), 2004) recently identified a subset of ISGs that are not induced in response to interferons (IFNs) in mouse embryonic fibroblast cells (MEFs) doubly null for the expression of I?B kinase a and ß (IKKa and IKKß). Induction of one such gene, ip-10, was undiminished in MEFs that stably expressed the super repressor of I?Ba, as was induction in p65 -/- MEFs, indicating that IKK dependence for induction of that gene was unrelated to NF?B activation. Further microarray work has revealed that the IFN-induced transcription of other IKK-dependent ISGs is specifically dependent on IKKß expression. In an experiment conducted using CodeLink technology, of 584 ISGs induced in a pool of IKKß-/- cells stably restored for IKKß expression, 370 (63%) were not induced in IKKß/- - cells. Several of these genes have been confirmed by Northern analysis. We hypothesize that IFN? activates IKKß to produce a distinct signal, unrelated to NF?B activation, that leads to the activation of as of yet unknown transcription factors, thus helping to stimulate the transcription of a subset of ISGs. We are currently working to identify upstream signals that activate IKKß by IFNs, the factors downstream of that event, and the cis-regulatory elements required for the IKKß-dependent response of certain ISGs. |
1. Title: Lead Screening: Attitudes and Practices of Cuyahoga County Primary Care Providers

2. Student Presenter: Amy Silverberg

3. Co-workers and Collaborators: Leila Jackson, Margaret Pizzi, Matthew Carroll, Terry Allan

4. Advisor: Dorr Dearborn

5. Departments: Department of Environmental Health Sciences, Swetland Center for Environmental Health, Department of Epidemiology and Biostatistics

6. Institutions: Case Western Reserve University School of Medicine, University Hospitals, Cleveland Department of Public Health, Cuyahoga County Board of Health

7. Support: Greater Cleveland Lead Advisory Council, HUD Healthy Homes grant OHLHH0141-05, QualChoice, CareSource

8. Please choose your academic program: MD

9. What year are you in the program? 2

10. Body of Abstract (300 words or less) Childhood lead exposure remains a serious environmental health problem in the Cleveland area, especially for poor families, because of the age and condition of available housing. While at high levels lead can make exposed individuals obviously sick, the more common lower level exposures close to and even below the CDC’s 10 µg/dl level of concern can have more subtle effects, including long-term and potentially permanent cognitive impairment and behavior problems. New cases of children with elevated blood lead levels continue to be diagnosed at an alarming rate in Cuyahoga County while state Medicaid records show that large numbers of children who by law should be screened by their physicians are not being screened. Recognizing that by the time a child tests positive for an elevated blood lead level, some of the damage has already been done, a widely used screening program is still an important part of eliminating childhood lead poisoning since it serves to raise awareness, to alert families and their physicians more quickly to potential problems, and to pinpoint sites for potential remediation. We distributed a survey to 1900 primary care providers in Cuyahoga County to learn more about their attitudes and practices regarding lead screening. The goal of the project is to better understand the barriers faced by physicians and their patients which are preventing large numbers of children from being screened. The surveys are currently being returned, and preliminary data will be analyzed over the next few months.
| 11. What was your role in this project? | I created the survey and did some of the coordinating of the mailing. I will be overseeing/doing the data entry and will participate in data analysis. |
**SIMMONS, DAEMON**

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Cell Surface Marker Response to BCG Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Daimon Simmons</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Nicole Pecora</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Cliff Harding</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Pathology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>It has previously been shown in vitro that infection of mouse immune cells with Mycobacterium bovis (BCG) results in down-regulation of Class II MHC. Now we examine this phenomenon with an ex vivo model in which expression levels are compared in immune cells from naïve mice and BCG-infected mice through flow cytometry. Levels of MHC-II and TLR-2 both appear to increase globally in some populations of cells upon infection, and infected cells may increase or decrease levels of these proteins depending on which population they belong to. Finally, examination of one of the cell surface markers (CD11B) used to distinguish these different subpopulations, reveals that the levels of expression of these cell surface markers also change in cells infected with BCG. The in vitro experiment shows cells infected with BCG concurrently decrease levels of CD11B and MHC-II.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>I ran the pilot experiment which suggested that cell surface marker changes may be occurring.</td>
</tr>
</tbody>
</table>
### 1. Title
The Purine Receptor P2RY2 is a Modifier of BMI in Cystic Fibrosis

### 2. Student Presenter:
Sarah Smith

### 3. Co-workers and Collaborators:
John Dunn

### 4. Advisor:
Mitchell Drumm, Ph.D.

### 5. Departments:
Department of Pediatrics, Division of Pulmonology

### 6. Institutions:
Case Western Reserve University School of Medicine

### 7. Support:
This work was supported by grants from the Cystic Fibrosis Foundation and NIH HL-68890

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)
Variation in cystic fibrosis severity between individuals with identical Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) mutations has been partially attributed to polymorphisms in genes that modify the severity of disease. One measure of disease severity in cystic fibrosis is body mass index (BMI), with low BMI correlating with poorer clinical outcomes. Low BMI is often attributed to pancreatic insufficiency, but it is also possible that polymorphisms in modifier genes have independent effects on BMI. As part of a search for new genetic modifiers, polymorphisms in the 5’ untranslated region of P2RY2 were identified as correlating with BMI in 808 patients within the Cystic Fibrosis Gene Modifier Study homozygous for the ?F508 CFTR mutation. P2RY2 encodes a G-protein-coupled purine receptor that by mobilizing intracellular calcium exerts a variety of effects, including activation of chloride channels in epithelia and mediating leukocyte chemotaxis. Individuals homozygous for a rare P2RY2 allele were approximately 3 times as likely to have healthy BMIs as those who were homozygous for the common allele, and BMI was on average 2 points higher. This study was replicated in a local population of 237 patients with several CFTR mutations, and those who were homozygous for the rare P2RY2 allele were found to be 2 times as likely to have a healthy BMI and the average BMI was 1 point higher. In order to determine whether the rare allele influences the quantity of P2RY2 transcript, we performed qPCR on cDNA from lymphocytes of 15 patients homozygous for the P2RY2 variants. Those with the common genotype had approximately twice as much P2RY2 RNA, (p=0.1, student t-test). These qPCR data are preliminary, but suggest that the rare allele at this polymorphic site might have a favorable effect on BMI in CF patients due to lower expression of the P2RY2 receptor.
| 11. What was your role in this project? | collected and analyzed data |
Introduction: Models of human cortisol production suggest that a circadian rhythm and a pulsatile rhythm may operate independently to release ~5-12 mg/m2/day of cortisol. The pulsatile nature of cortisol secretion may play a role in the regulation of cytokines. Our aim was to compare the cytokine response in healthy volunteers to a continuous or pulsatile cortisol infusion.

Methods: Twenty healthy volunteers were given either a continuous cortisol infusion over 6 hours at the rate of 1.5 mcg/kg/min or a pulsatile infusion over 6 hours consisting of four, twenty-minute pulses of 135 mcg/kg, for an equivalent total dose on a weight basis. Peripheral blood was taken before and after the cortisol infusion, stimulated with 0.1 ng/ml of endotoxin, and evaluated for release of various cytokines.

Results: Data from certain cytokines such as TNF-alpha validated our methodology. Interestingly, ICAM-1 was increased in all volunteers after cortisol infusion (p = .001). The increase in the pulsatile group was statistically significant (p = .036) while the increase in the continuous group was not (p = .123). MIF was increased in both groups after cortisol infusion (p=.077), with a statistically significant increase in the continuous group (p = .007) compared to the pulsatile group (p=.594).

Discussion: Our data demonstrate that ICAM-1 is upregulated within hours of cortisol exposure. In addition, MIF may be up-regulated in response to cortisol exposure. Furthermore, it seems that the mode of cortisol infusion may have an impact on cytokine response. These novel findings need to be confirmed in larger trials.
<p>| 11. What was your role in this project? | Designed and performed study and analyzed data |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Radiologists’ Attitudes Toward Mammography and the Link to Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Hee Yon Sohng</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Joann Elmore</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Medicine</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>University of Washington; University of Vermont; Oregon Health Sciences University; University of California, San Francisco; Center for Health Promotions Research, Group Health Cooperative</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Are Mammographers Who Enjoy Or Report Being Good at Mammography Actually Better?  
Introduction  
A recent Institute of Medicine report predicts a shortage of radiologists reading mammograms. Fellowships and positions in breast imaging practices are unfilled (29% of 570) and specialists are not recommending the field as a career. Among those who do read mammograms, there is extensive variability in interpretive accuracy. This study examines the relationship between radiologists’ interpretive accuracy and their perceptions of and attitudes toward mammogram interpretation.  
We aim to:  
1) Describe radiologists who enjoy interpreting mammograms and those who report being good at interpretation.  
2) Examine associations between radiologists’ enjoyment and interpretive performance of mammography.  
Methods  
We have linked data from community radiology practice sites in three geographical regions in the U.S. Screening and diagnostic mammogram (n = 725,860) data interpreted by 126 radiologists from 1994 to 2004 was linked to survey responses that assessed professional satisfaction. Generalized estimating equations were developed to model abnormal interpretation rates and cancer detection.  
Results  
57% of radiologists enjoy and 91% believe they are good at interpreting mammograms. Women (93%) more than men (46%), enjoy interpreting mammograms, as do those who interpret over 2,000 mammograms/year, |
are salaried, or are affiliated with an academic institution. Radiologists who enjoy interpreting mammograms are more likely to think they are good (p<0.01).
Radiologists who enjoy interpreting mammograms recalled fewer screening mammograms (p<0.05). Those who believe they are good at interpreting had a higher abnormal interpretation rate and detected more cancers, 39.7 cancers found per 1,000 exams, compared to 33.5 detected (p<0.05).

Conclusions
Job satisfaction is a predictor for staying in a job and recommending the same work to residents. Our study found that radiologists who enjoy mammography perform better and identified practice and physician characteristics associated with increased enjoyment.

| 11. What was your role in this project? | second author |
## SOPKO, NIKOLAI

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Increased Accuracy of Pulmonary Imaging using Sub-Regional Analysis via Three Dimensional Volume Warping</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Nikolai Sopko</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Zhenghong Lee</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Biomedical Engineering</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Computerized Tomography (CT) provides excellent three-dimensional anatomical information by making use of the inherent variance of densities between tissues found in the human body. Its acuity for imaging dissection is strongest for denser structures, namely bone and organ parenchyma. Human lungs can occupy a quarter of total body volume and facilitate oxygen equilibration between outside air and our blood by providing a large surface area for gas exchange. Therefore the corresponding form to this function is one of air filled sacs surrounded by thin layers of tissue with very low density. Hence, healthy lungs are “transparent” to x-rays. In order to visualize the fissures that separate lung lobes and obtain a more accurate position within the lung, a high intensity CT scan must be used, which greatly exceeds normal x-ray exposure and could significantly increase health risks due to radiation especially in individuals that need multiple scans within a short period of time. Lung models, which provide precise anatomical landmarks, have been developed by averaging high intensity CT scans of healthy volunteers. We used such a lung model by warping its volume to several juvenile CT scans using a control point algorithm, which gave us lobular definition in our patient’s normal resolution CT. One of the many advantages of this technique is its use in conjunction with Single Photon Emission Tomography (SPECT). We used these combined modalities to monitor acute inflammations in cystic fibrosis (CF) patients by tagging polymorphic nuclear cells (PMN) with a radioactive anti-body that SPECT could detect and simultaneously locating their aggregations within lobular regions of the lung using our CT warping technique. Patients underwent two imaging regimens that were pre and post IV antibiotic treatment. We compared pulmonary function tests with PMN activity determined by SPECT/CT regional analysis and we obtained mixed results.</td>
</tr>
</tbody>
</table>
Healthcare resource changes may affect the health outcomes of patients, especially when occurring rapidly and in economically vulnerable communities. This study assessed health care access, utilization, and health status following the closure of four hospitals in Cuyahoga County between 1998 and 2004 and examined whether a disproportionate effect was observed among the most economically disadvantaged residents.

We examined three waves of data on Cuyahoga County residents (sample sizes: 1495, 1420, and 3410) participating in the Ohio Family Health Survey. Trends on insurance and general health status, the presence of a usual source of care, and health care utilization were correlated with patient demographics and hospital utilization statistics. Respondent income (poor <100% Federal Poverty level [fpl], near-poor 100-200% fpl and not poor >200% fpl) was used in stratified analyses to assess its relationship with health outcomes during the period studied.

Although basic demographics across cohorts remained stable, educational attainment, annual income, Medicaid enrollment (12.0% vs. 15.2%) and poverty levels (14.7% vs. 18.3%) all increased over time, suggesting increasing income inequality. The proportion with unmet health care needs and poor health status both increased, especially among the near-poor - the only group to report no increase in having a usual source of care. Hospital admissions dropped initially following the hospital closures, while occupancy rates increased.

A short-term decrease in access to care related to hospital closures and a decline in health status among study participants raises questions about the ability of remaining hospitals to meet the needs of county residents. While Medicaid expansion may have affected the availability of usual
sources of care and helped to buffer the effects of these closures, the near-poor were not aided by this expansion. Future policy initiatives are needed to specifically target this subset of individuals who are not currently eligible to access safety net services.

<p>| 11. What was your role in this project? | Formulating questions, collecting data, and interpreting results |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>The Effect of Age on Exercise Guideline Adherence in Men and Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Beth Stepanczuk</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Mary A. Dolansky, RN, PhD, Jacqueline M. Charvat, MS, Shirley M. Moore, RN, PhD</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Shirley M. Moore, RN, PhD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Frances Payne Bolton School of Nursing</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td></td>
<td>Frances Payne Bolton School of Nursing</td>
</tr>
<tr>
<td></td>
<td>School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>American Federation for Aging Research - MSTAR Program</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Background: The purpose of this secondary analysis was to determine if age affects women and men's exercise guideline adherence after completion of a cardiac rehabilitation program (CRP).</td>
</tr>
<tr>
<td></td>
<td>Methods: The primary randomized control study examined the effect of an intervention which aimed to increase exercise maintenance after a CRP. The sample consisted of 248 adults 38-86 years old. Exercise patterns were recorded by heart rate monitor wristwatches worn during exercise sessions for 48 weeks following a CRP.</td>
</tr>
<tr>
<td></td>
<td>Results: Survival analysis methods were employed in this study, using the non-adherence event as the week following the last time that a participant did not meet the guideline of 3 exercise sessions per week. While no differences were found in adherence between the age groups for women, older men were 41% more likely to become non-adherent sooner than younger men, even when controlling for fitness level, pain, comorbidity, self-efficacy, depressed mood, and social support.</td>
</tr>
<tr>
<td></td>
<td>Conclusion: Non-adherence rates were higher for older men compared to younger men. Because less than 37% of all CRP participants continued to adhere to exercise guidelines at 1 year, interventions to maintain exercise after completion of a CRP are needed to maintain health benefits.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>Research Assistant</td>
</tr>
</tbody>
</table>
1. Title | Knowledge Is Power: Educating Uninsured Patients Living with Diabetes in Greater Cleveland

2. Student Presenter: | Jonah Stulberg, M.P.H.


4. Advisor: | Susan Flocke, Ph.D.

5. Departments: | Epidemiology and Biostatistics, Family Medicine

6. Institutions: | Free Medical Clinic of Greater Cleveland, Case Western Reserve University

7. Support: | Crile Summer Fellowship, 2005

8. Please choose your academic program: | MD PHD

9. What year are you in the program? | 2

10. Body of Abstract (300 words or less) | Background: Rapidly increasing numbers of uninsured individuals are turning to safety net organizations for ongoing care of Type II Diabetes. Formal patient education and patient empowerment curriculum are currently lacking but critically needed. This study evaluates the efficacy and effectiveness of a new diabetes education program implemented in the Free Medical Clinic of Greater Cleveland (Free Clinic).

   Methods: The Knowledge is Power diabetes education program was designed specifically to meet the needs of the patients of the Free Clinic and to fit the natural patient flow of the clinic. 37 participants enrolled and received 9 hours of education. Evaluation outcomes included: attendance rates, satisfaction with the course, readiness to change, change in participant knowledge and staff impressions of program effectiveness. A planned review of the medical records of participants and a sample of non-participants will assess fasting blood glucose, hemoglobin A1C, blood pressure and consistency of medication refills at four time points: baseline, completion of the program, and three- and six-months after the intervention.

   Results: Initial analysis suggests the Knowledge Is Power program was feasible in this setting and successful in motivating participants to make productive changes in their health care habits. The program achieved over a 50% retention rate, a 10 fold increase over previous programs in this setting. Participant satisfaction was high. Anecdotally, the Free Clinic staff report higher medication adherence rates and a higher level of engagement in self-care by program participants. The medical record review is scheduled for the last week in March so that all program groups will have 6 month results.
Conclusions: Though complete results are currently pending, the findings reported thus far were positive enough to encourage the Free Medical Clinic of Greater Cleveland to pursue future Knowledge Is Power classes and stimulated development of ongoing diabetes support groups. If this program has an effect on important biomedical markers, it could be implemented to meet the needs of patients with diabetes seeking care in other safety net clinics.
# Alzheimer's disease pathology mediated by gonadotropins

## Title
Alzheimer's disease pathology mediated by gonadotropins

## Student Presenter:
Stephanie Tarkowsky

## Co-workers and Collaborators:
Gemma Casadesus1, Kate M. Webber1, Christopher W. Gregory3, Richard L. Bowen 3,5, Craig S. Atwood2, George Perry1,4 and Mark A. Smith1.

## Advisor:
Mark A. Smith

## Departments:
Pathology

## Institutions:
1Department of Pathology, Case Western Reserve University, Cleveland, Ohio; 2School of Medicine, University of Wisconsin and William S. Middleton Memorial Veterans Administration, Madison, WI; 3Voyager Pharmaceuticals Corporation, Raleigh, NC; 4College of Sciences, University of Texas at San Antonio, San Antonio, TX. 5Current Address: Raleigh NC

## Support:
AFAR, Culpepper Fellowship

## Please choose your academic program:
MD

## What year are you in the program?
2

## Body of Abstract (300 words or less)
Age-related increases in luteinizing hormone (LH) have recently been implicated in the etiology of Alzheimer disease (AD), particularly in mechanisms involving amyloid-ß synthesis and deposition. To further explore the potential pathophysiological mechanisms involved in the actions of LH in AD, we used an in vitro model system (SH-SY5Y) to examine the effects of LH on oxidative stress, cell signaling, and tau phosphorylation. Our data demonstrates that LH dose-dependently leads to increases in tau phosphorylation, ERK activation, and increases in the activity of GSK-3ß. Importantly, similar doses also lead to redox changes including increased cellular stress as shown by increases in oxidized cellular glutathione (GSH) levels. These results indicate that LH is likely to be pluripotent mediator of the disease since, in addition to modulating amyloid-ß-related mechanisms, LH also mediates redox and cytoskeletal imbalances associated with the modulation of endogenous antioxidant systems such as GSH and aberrant tau phosphorylation. Moreover, since high LH levels were associated with ERK phosphorylation and GSK-3ß, it is likely that LH may, at least partially, work via cell signaling mechanisms involving mitogenic pathways.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11. What was your role in this project?</strong></td>
<td><strong>Research Assistant - I cultured the cells, ran the blots, and performed the immunochemistry</strong></td>
</tr>
</tbody>
</table>
Preterm children suffer from multiple neurological deficits. Although a component of damage involves the loss of neural cells early in development, the molecular mechanisms of injury have not been fully elucidated. The subplate, a transient layer just below the immature cerebral cortex, houses neurons that differentiate and form networks prior to the differentiation of projection neurons in the cortex. In humans presumably, the subplate has its greatest impact on cortical development when it reaches its maximal thickness at 25-26 weeks, a frequent point of preterm birth. We hypothesize that preterm babies will show an inappropriate early loss of subplate neurons resulting in disturbed neurological function. We evaluated biopsies taken from fetuses with evidence of incorrectly formed cortices for immunohistochemical changes different from subplates taken from fetuses expired by non-CNS related cause. IRB approved anatomically matched specimens were labeled with markers of neuronal development using immunohistochemistry. An experienced neuropathologist blinded to the results of our immunohistochemistry reviewed the samples for standard signs of perinatal brain injury. Samples without significant brain damage were labeled controls. Preliminary results showed marked differences between the controls and the fetuses with brain damage. The final analysis involves comparing the differences between preterm infants and controls using two-tailed t test or one-way ANOVA for parametric variables, and the Chi square test for non-parametric variables. Differences with p<0.05 will be considered significant.
<p>| 11. What was your role in this project? | Research Intern |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Multiple Substitutions at Ambler Position 244 in SHV ß-lactamase Provide Insight into Importance of Arg244 in Inhibitor and Substrate Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Jodi M. Thomson</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Anne M. Distler, Fabio Prati</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Robert A. Bonomo</td>
</tr>
<tr>
<td>5. Departments:        Department of Pharmacology, Division of Research Service, and the Department of Chemistry,</td>
<td></td>
</tr>
<tr>
<td>6. Institutions:         Case Western Reserve University School of Medicine, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, and the University of Modena, Modena,</td>
<td></td>
</tr>
<tr>
<td>7. Support:             Jodi Thomson was supported in part by NIH T32 GM07250 and the Case Medical Scientist Training Program. Special thanks to the National Institutes of health for</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD PHD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>5</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less)                              | Background: Inhibitor resistant class A ß-lactamases are an emerging threat to ß-lactam/ ß-lactamase inhibitor treatment of gram negative infections. Based on clinical isolates of inhibitor (clavulanate) resistant TEM enzymes with mutations at Ambler position Arg244, we used site-saturation mutagenesis to explore the importance of this residue in substrate and inhibitor binding and recognition in SHV, an enzyme found most notably in the hospital pathogen Klebsiella pneumoniae.  

Materials and methods: We constructed 19 mutants at position 244 by site-saturation mutagenesis of the blaSHV-1 gene. Agar dilution MICs were performed on all isolates. Enzymes were expressed in Escherichia coli DH10B and purified using preparative isoelectric focusing. Steady state kinetics were performed and Ki and kinact values determined through competition with the substrate nitrocefin. Mass spectrometry was performed on SHV-1 and SHV R244S with and without clavulanate inactivation, and tryptic digests of the inhibitor/ ß-lactamase complexes were performed and analyzed.

Results: 16 variants at Arg244 had increased MIC values against ampicillin/clavulanate. In contrast, all 19 mutants had decreased MIC values to ampicillin, cephaloridine, and piperacillin. Kinetic studies on clavulanate resistant variants Arg244Ser, -Gln, and -Glu showed a decrease in affinity for both inhibitor and substrates (60-1000 fold lower than SHV-1). Unexpectedly, the kinact values of the mutants were all
Paradoxical increase in sulbactam susceptibility among a panel of clavulanate resistant SHV beta-lactamase mutants at Ambler position 244.
had been regenerated by 15 minutes. In contrast, intact R244S is barely detectable at this time point, with prominent peaks representing 70 and 88 dalton adducts. To further our study of this interesting panel of mutants, we studied novel penem inhibitors and probed their ability to inactivate SHV-1 and the R244 mutants. Compared to clavulanate and the sulfones, turnover of the penem inhibitors by all enzymes was strikingly low (<2 inhibitor molecules per 24 hours). In addition, mass spectrometry experiments indicate that these inhibitors do not exhibit fragmentation within the active site of SHV-1 or R244S as is seen with sulbactam and tazobactam.

11. What was your role in this project? primary author (I did all experiments, but didn't synthesize the compounds we studied)
TOOGOOD, PAUL

<table>
<thead>
<tr>
<th>1. Title</th>
<th>A Comparison of Periarticular Tibial Plate Fits on Normal Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Paul Toogood</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Goyal, KS; Marcus, RE; Vallier, HA; Haille Sallasse, J.</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Daniel Cooperman</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Orthopaedic Surgery; CWRU-SOM</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>CWRU-SOM, University Hospitals of Cleveland, Metrohealth Medical Center; Cleveland Museum of Natural History</td>
</tr>
<tr>
<td>7. Support:</td>
<td>CWRU-SOM (Crile Fellowship)</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD MS</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | A variety of surgical plates for fixation of proximal tibial fractures are currently available. A plate whose contours minimize space between itself and the bone and whose axes align with those of weight-bearing is desirable to minimize impingement on surrounding tissue and intimately secure fracture fragments.

This study attempted to quantify fit amongst three different, widely available lateral proximal tibial plates (Zimmer Non-locking, Synthes Non-Locking, Synthes Locking) on 100 normal humans to test each plate’s ability to fit a random sample and to examine differences amongst the three systems.

The study utilized right tibias of 25 white males, 25 white females, 25 black males, and 25 black females made available from the Hamann-Todd Osteological Collection. Each of the plates was secured to each tibia in "best-fit" orientation and measurements taken with a Microscribe G2LX and Rhinoceros software to determine the plate’s alignment with the tibial plateau and shaft and the amount of space between the plate and the bone in total, as well as in defined proximal, middle, and distal surfaces of the plate. If the average distance between the plate and tibial surface in the middle and distal regions was within 1mm of each other the plate was said to fit evenly, otherwise the fit was spanned (middle > distal) or impinged (middle < distal). An anatomic fit was defined as an average total distance of less than 1.5mm, plus an even fit, plus a plateau and shaft alignment of less than 2 degrees.

Out of 100 tibias, 7 Zimmer Non-Locking, 9 Synthes Non-Locking, and 3 Synthes Locking met the criteria for anatomic fit. This translates into the
majority of tibia having large volumes, spanned/impinged fits, or poor alignment. Such findings suggest the importance of objectively defining "anatomic fit", a term applied by most manufacturers of contemporary plating systems.

| 11. What was your role in this project? | Data Collection and Project Design |
Thyroid hormone (T3) hyper-secretion has well-documented effects in humans. At the heart level, hyperthyroid hormone production results in a switch in the myosin heavy chain isoform expression, and an increase in both adrenergic responsiveness and heart contractility via modulation of phospholamban and associated SERCA pump. At the pharmacological level, beta-blocker therapy only provides a partial amelioration of some of these symptoms, thus suggesting that some of the thyroid hormone-induced modifications within the cardiac myocytes are long-lasting and not simply reconducible to beta-adrenoceptor activity and responsiveness. Possible explanations include inhibition of β-adrenergic cascade inhibitors, upregulation of β-adrenergic stimuli by thyroid hormone, and increase in the expression of the β-adrenergic receptor subtype 1.

We tested the hypothesis that an increase in circulating T3 affects cation distribution within cardiac cells and possibly systemically. The data obtained indicate that male Sprague-Dawley (~300g) rats rendered hyper-thyroid by 3-4 administrations of T3 or T4 presented ~25% increase in total magnesium (Mg2+) content within cardiac ventricular myocytes. In contrast, rats rendered hypothyroid presented a ~20% decrease in total Mg2+ content. Similar changes were also observed in the serum and liver tissue. The administration of specific β-adrenergic agonists (e.g. isoproterenol) or cell permeant cyclic-AMP analogs (e.g. 8-Cl-cAMP) resulted in a 25% and 35% increase in the amount of Mg2+ extruded into the circulation from the hearts of T4 and T3-injected rats, respectively. My next step was to determine Mg2+ distribution within cardiac myocytes. One model consisted in isolating cardiac ventricular myocytes from hyperthyroid animals by collagenase-digestion. The second model consisted in reproducing hyper-thyroid conditions in the H9C2 cardiac...
myocyte cell line. The preliminary results indicated that H9C2 cells needed to be treated for ~96 hours with daily administrations of T3 to present a detectable increase in cellular Mg2+ content that was similar to the increase observed in collagenase-dispersed myocytes isolated from hyperthyroid rats.

11. What was your role in this project? conducted research
1. Title | Self reported health characteristics of adult smokers and non-smokers exposed to environmental tobacco smoke
---|---
2. Student Presenter: | Lauren Tuchman
3. Co-workers and Collaborators: | 
4. Advisor: | Elaine Borawski
5. Departments: | Epidemiology and biostatistics
6. Institutions: | Case Center for Health Promotion Research and the Ohio Tobacco Research and Evaluation Center (OTREC)
7. Support: | 
8. Please choose your academic program: | MD
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | Objective: To assess self-reported health characteristics of adult smokers and non-smokers exposed to environmental tobacco smoke.

Methods: This study used the 2004-06 Cuyahoga County BRFSS, which involves 1200-1500 adults each year (n=4,127). The data are weighted to reflect the population of Cuyahoga County. The telephone-based survey includes questions on current smoking behaviors and exposure to environmental tobacco smoke (ETS) at home and in cars.

Respondents were divided into 4 groups: non-smokers without exposure to ETS, non-smokers with exposure to ETS, smokers without exposure to ETS, and smokers with exposure to ETS. Using GLM, the 4 groups were compared on: history of heart attack, angina or coronary heart disease, stroke, high cholesterol, hypertension; current use of hypertension medications; current diagnosis of asthma; children with asthma; loss of 6 or more teeth; and self-rated health. All analyses controlled for age, gender, race, education, income, and health insurance.

Results: Among non-smokers, those exposed to ETS were more likely than those not exposed to: report hypertension (32% vs. 23% without exposure); take hypertension medications (26% vs. 23%); have children with asthma (24% vs. 15%); and have lost 6 or more teeth (17% vs. 14%).

Among smokers, those exposed to additional ETS were more likely than those who were not exposed to additional ETS to: have had a heart attack (4% vs. 1%); been told they have hypertension (23% vs. 20%); to be currently taking hypertension medication (17% vs. 13%); to have high cholesterol (45% vs. 20%); to have children with asthma (22% vs. 19%);
to have lost 6 or more teeth (22% vs. 17%), and to rate their health fair or poor (21% vs. 17%).

Conclusions: Exposure to secondhand smoke seems to be associated with negative health consequences and the development of many diseases, above and beyond the personal smoking habits of the individual.

| 11. What was your role in this project? | Data analysis. Survey design for future surveys. |
## Design and testing of a mast cell culture platform for STAT5 structure-function studies

### 2. Student Presenter:
- **John Tuttle**

### 3. Co-workers and Collaborators:
- **Geqiang Li**

### 4. Advisor:
- **Kevin D. Bunting**

### 5. Departments:
- **Department of Medicine, Division of Hematology-Oncology**

### 6. Institutions:
- **Case Western Reserve University**

### 7. Support:
- **National Institutes of Health Grants R01DK059380 and R01HL073738**

### 8. Please choose your academic program:
- **MD MS**

### 9. What year are you in the program?
- **2**

### 10. Body of Abstract (300 words or less)

Signal Transducer and Activator of Transcription 5 (STAT5) is a critical transcription factor required for many aspects of hematopoietic development and its dysregulation leads to hematologic disease in mice and humans. Therefore, better understanding of how it functions to drive gene expression is of importance to the medical field. The Bunting lab has developed a novel system to study STAT5 structure-function in STAT5abNull/null mast cells, which are generated from day 14.5 fetal livers. Utilizing retrovirus-mediated gene transfer, the cells can be genetically manipulated to add-back particular STAT5 mutants designed to pinpoint structure/function relationships. The STAT5Null/Null mast cells transduced with an empty control vector provide a negative control for this system; STAT5Null/Null mast cells retrovirally reconstituted with wild-type STAT5a serve as a positive control. One application of this platform is to study the role of post-translational modification of STAT5 (phosphorylation/glycosylation) on transcriptional activity. STAT5 has been shown to be serine phosphorylated in certain circumstances; however, the role of serine phosphorylation in STAT5 function has remained largely unknown. In my studies I found that adhesion of mast cells to fibronectin led to STAT5 serine phosphorylation at both serine 725 and serine 779 in a time dependent manner. Mutation of both serines abolished the fibronectin-induced STAT5 phosphorylation. This is the first demonstration that STAT5 interactions with extracellular matrix can lead to post-translational modification. The impact of serine phosphorylation on STAT5 migration function is ongoing. In conclusion, this new method will allow further characterization of STAT5 mutants, leading to a unique and powerful experimental platform for investigating the morphology, survival, and migration of a cell type that plays integral roles in innate and adaptive immune responses of relevance in allergy, infection, and immune
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. What was your role in this project?</td>
<td>Performed experiments</td>
</tr>
</tbody>
</table>
1. Title | Re-expression of thrombospondin-1 using 5-AZA-2’-deoxycytidine: Effects on tumor angiogenesis in melanoma
---|---
2. Student Presenter: | Masumi Ueda
3. Co-workers and Collaborators: | Barbara Jacobs, Rebecca Haney, Dr. Daniel Lindner
4. Advisor: | Dr. Ernest Borden
5. Departments: | Center for Hematology and Oncology Molecular Therapeutics
6. Institutions: | Taussig Cancer Center, Cleveland Clinic Foundation
7. Support: | Crile Fellowship
8. Please choose your academic program: | MD
9. What year are you in the program? | 2
10. Body of Abstract (300 words or less) | The epigenetic silencing of genes by DNA methylation of promoters is an important element in the progression of neoplastic processes. Aberrant silencing of genes that regulate cell proliferation can result in uncontrolled tumor growth. Thrombospondin-1 (TSP-1) is an endogenous angiogenesis inhibitor that blocks endothelial cell migration and proliferation. Studies have shown increases in gene expression of TSP-1 in cancer cell lines after treatment with 5-AZA-2’-deoxycytidine (5-AZA-dC), a well-established DNA demethylating agent. Because angiogenesis is critical for tumor growth, epigenetic silencing of TSP-1 may contribute to tumor cell proliferation. We hypothesized that the re-expression of TSP-1 through demethylation with 5-AZA-dC would restore its anti-angiogenic effects.

Gene expression of TSP-1 in human melanoma cell lines (A375, SKMEL3, and WM164) after treatment with 5-AZA-dC (0.2 µM, 4 days) were compared to untreated cells. Quantitative RT-PCR was performed from total RNA isolated. Results showed a 20-fold increase in the expression of TSP-1 in WM164 cells after 5-AZA-dC treatment but no increase in A375 or SKMEL3 cells. Treatment with 5-AZA-dC (0.2 µM) for 8 days showed a 53-fold increase in the expression of TSP-1 in WM164 cells compared to control. Protein expression was examined using whole cell lysates in western blotting. No bands specific for TSP-1 were detected in control or treated A375, SKMEL3, and WM164 cells.

Currently we are investigating the effects of 5-AZA-dC treatment on angiogenesis in mouse xenograft models by utilizing an intradermal assay to assess host vascularization of implanted tumors. We are comparing angiogenesis in inoculated WM164 tumors after 5-AZA-dC treatment in
vitro to no treatment by quantifying the number of blood vessels touching the circumference of tumor nodules.

Although functional correlation remains to be established, we have identified increases in TSP-1 gene expression in WM164 melanoma cells after treatment with an inhibitor of promoter methylation.

| 11. What was your role in this project? | Planning and conduction of experiments under direction of advisor |
### 1. Title

### 2. Student Presenter:
Michael Vander Meulen

### 3. Co-workers and Collaborators:
Kiprotich Chelimo, Peter Odada Sumba, Nancy Fiore, Christopher Yohn, Rosemary Rochford

### 4. Advisor:
Ann M. Moormann

### 5. Departments:
Center for Global Health & Diseases  
Center for Vector Biology and Control Research  
Department of Microbiology & Immunology

### 6. Institutions:
Case Western Reserve University  
Kenya Medical Research Institute  
SUNY UpState Medical University

### 7. Support:
T35 training grant (Doerschuk)  
NIH K08 AI 51565 (Moormann)  
R01 CA102667 (Rochford)  
UO1 AI43906 (Kazura)

### 8. Please choose your academic program:
MD MPH

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)
Endemic Burkitt lymphoma (eBL) is the most prevalent pediatric cancer in equatorial Africa. Holoendemic Plasmodium falciparum (Pf) malaria and early-age Epstein-Barr virus (EBV) infection are two co-factors associated with eBL incidence. The role of EBV in tumorigenesis has been well described, however the impact of malaria co-infections on EBV persistence and reactivation are not so well understood. Previous cross-sectional studies support the notion that malaria suppresses EBV-specific T cell immunity. The highest EBV viral loads are present in children under 5 years of age living in malaria holoendemic areas, compared to the lowest viral loads in older children and children infrequently infected with malaria. In order to further elucidate the longitudinal interaction between these co-infections, EBV viral load was measured in repeat cross-sectional samples from the same children living in areas of Kenya with divergent malaria transmission. T cell immunity is also important for controlling another persistent herpes virus infection, Cytomegalovirus (CMV) that is not associated with eBL. Therefore CMV and EBV viral loads were compared by RTQ-PCR from whole blood DNA isolation. We found 67% (158/236) EBV+ and 17% (38/221) CMV+ samples at baseline with an inverse age correlation. Two 2 years later, 40% (70/174) of these children were EBV+ and 4% (7/171) were CMV+ suggesting the development of immune control over these persistent viral infections. When dichotomized by malaria exposure, the youngest
children from the holoendemic area had the highest mean EBV viral loads. There was no correlation between CMV and malaria. Of note was the proportion of children with consistently high EBV viral loads, similar to levels previously reported for children with eBL. Ongoing longitudinal studies will determine if continually high EBV in peripheral blood is a risk factor for eBL.

11. What was your role in this project?

Perform experiments and interpret data.
**Title**: Prognostic Significance Of Left Atrial Appendage Sludge In Patients With Atrial Fibrillation

**Student Presenter**: Brandon Varr

**Co-workers and Collaborators**: Boris Lowe MD

**Advisor**: Allan Klein MD

**Departments**: Section of Cardiovascular Imaging, Department of Cardiovascular Medicine

**Institutions**: Case Western Reserve University, The Cleveland Clinic Foundation

**Support**: T-35 grant

**Academic Program**: MD

**Year in Program**: 2

**Body of Abstract (300 words or less)**

**OBJECTIVE**: To assess the mortality of patients with atrial fibrillation (AF) and left atrial appendage (LA/AA) sludge.

**RATIONALE**: Patients with AF and LA/AA dense spontaneous echocardiographic contrast (SEC) or thrombus have an increased mortality and risk of cerebral thromboembolism. Thrombus stands as a contraindication to cardioversion, but there are no published studies on the fate of patients with LAA sludge to direct clinical management.

**METHODS**: Patients with AF undergoing transesophageal echocardiographic (TEE) evaluation prior to electrical cardioversion or radiofrequency pulmonary vein isolation were included in the retrospective case-control study. Sludge was defined as optically intense dynamic gelatinous consistency echodensities, without a discrete mass, in the LAA throughout the cardiac cycle. Event rate was all cause mortality.

**RESULTS**: A total of 127 patients with AF undergoing TEE evaluation prior to elective electrical cardioversion or radiofrequency pulmonary vein isolation with LA/AA thrombi, sludge, dense SEC comprised the study groups. Patients with AF, but without these echocardiographic risk factors, served as control patients. Interobserver agreement for the presence of sludge was kappa = 0.92. In the LA/AA, 27 patients (21%) had thrombi, 58 patients (46%) had sludge, and 42 patients (33%) SEC. In patients with LAA sludge, the event rate was 47% (p=0.019). Appendage thrombus was associated with a 59% event rate (p=0.003). This compares with an event rate of 25% in the control group.
CONCLUSIONS: Patients with AF and LAA sludge identified by TEE have a high likelihood of death. In the clinical management of these patients, sludge should be considered as evidence against undergoing cardioversion procedures.

<p>| 11. What was your role in this project? | Data procurement and classification of study groups. Some data analysis. |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Treatment of CD34+ Umbilical Cord Blood Stem Cells with Anaphylatoxin C3a Facilitates Transmigration Towards Stromal Derived Factor-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Marielena Vélez</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Dr. Nicholas J Greco, Aaron Victor</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Mary J Laughlin</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Medicine, Department of Pathology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University, School of Medicine, Case Comprehensive Cancer Center</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Heart, Lung, Blood, and Sleep Disorders Grant, Grant Nos. R21-HL 72362-01 and Ohio BRTT/WCI03-02 (Center for Stem Cell and Regenerative Medicine)</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Homing of bone marrow (BM) and umbilical cord blood (CB) CD34+ stem cells to BM niches after transplantation into irradiated leukemic patients has been shown to depend on many cytokines and soluble factors, including the matrix metalloproteinase MMP9, and stromal derived factor (SDF-1). Shortened engraftment time is associated with lower incidence of mortality, reduced morbidity, and a reduction in the rate of secondary infection. In mice, treatment of selected CD34+ cells from BM and CB with leukopheresis supernatants, containing fibronectin and the C3a complement protein, leads to enhanced transmigration to SDF-1 and in vivo engraftment, respectively. Transplantation patients receive cryopreserved/thawed grafts. Therefore, non-cryopreserved and cryopreserved/thawed total nucleated cell fractions, selected CB CD34+ cells and CD34 negative cells were treated with 10 ug/ml C3a or DMEM/1%HSA (control) in the presence of adherent fibronectin for 30 minutes. Cells were migrated towards 300 ng/SDF-1 at 37°C for four hours. A transmigration index was calculated by flow cytometry for CD133+ cell content using an aliquot of untreated cells from each treatment migrating towards SDF-1. Treatment of CB CD34+ cells with C3a increased transmigration SDF-1 by 30%. Separately, different subgroups of non-cryopreserved and cryopreserved/thawed cells in the same treatment groups were analyzed by SDS-PAGE-zymography to measure the secretion of functional MMP9. Cryopreserved/thawed CD34+ cells were found to produce less MMP9 than the non-cryopreserved CD34+ cells. As reduced oxygen levels are observed in the BM, further experiments compared the synthesis of MMP9: no differences were observed between normoxia and hypoxia. These findings prompt further</td>
</tr>
</tbody>
</table>
investigation into conditions that may reveal a differential migration of CB cells in response to different C3a treatments and foster approaches to stimulate the expression of molecules important for homing on cryopreserved stem cells. Importantly, whether the exposure of cryopreserved/thawed CD34+ cells to C3a will increase MMP9 synthesis is unknown.

| 11. What was your role in this project? | Did the experiments, ran the flow cytometry samples, worked on the analysis, wrote the abstract, all with lots of help from the lab supervisor |
Endoscopic Demonstration of Third Ventriculostomy in the Preserved Human Cadaver Brain

Ravi M. Venkatesh

Dr. Sunil Manjila, Dr. Alan R. Cohen

Dr. Alan R. Cohen

Pediatric Neurological Surgery

Rainbow Babies & Children's Hospital

T-35 grant

MD

2

Endoscopic neurosurgery has gained widespread popularity because it can be performed with minimal disruption of neural structures. Third ventriculostomy has become an effective method of cerebrospinal fluid diversion in non-communicating hydrocephalus. This procedure is now the treatment of choice for acquired aqueductal stenosis. The aim of our study was to develop a cadaver hydrocephalus model to elucidate the trajectory for endoscopic third ventriculostomy and to evaluate the relevant endoscopic anatomy.

Ten cadaver heads were embalmed and preserved in ethanol after flush-irrigation through cannulated carotid arteries and jugular veins. The vessels were then injected with siliconated dyes and then dissections were performed. A frontal burr hole was made and a 30\(^\circ\) angled endoscope lens was inserted into the frontal horn of each lateral ventricle through the brain parenchyma. Landmarks in the lateral ventricles such as the septum pellucidum, choroid plexus, anterior septal and thalamostriate veins, and the foramen of Monro were identified. The endoscope was passed though the foramen of Monro into the third ventricle, and the third ventricular floor was closely inspected to study the anatomy of the mammillary bodies, infundibular recess, optic chiasm, and optic recess. Additionally, the endoscope was navigated around and in front of the massa intermedia.

Using the cadaver models for teaching endoscopic ventricular surgery has been a frustrating experience for both educators and students. Not only are these heads expensive and difficult to procure, transport, and preserve, but recreating the dilated ventricular system of hydrocephalus is also a challenge. The cadaver brains selected for reproducing
Ventriculomegaly must be fresh and soft. Ventricles are usually small and shrunken in older, firm, fixed or autolyzed brain specimens, rendering ventriculoscopic navigation extremely difficult. The author has succeeded in producing a viable model of ventricular cannulation, demonstrating the proper trajectory for skill-training in third ventriculostomy.

| 11. What was your role in this project? | Primary researcher in designing the protocol and executing the procedures |
**Title**
Effectiveness of Homebound Primary Care In Preventing Avoidable Hospitalizations in Chronic Disease Management

**Student Presenter:**
Parag Vora

**Co-workers and Collaborators:**

**Advisor:**
Dr. Steven Landers

**Departments:**
Department of Family Medicine

**Institutions:**
Case Western Reserve University, University Hospitals Health Systems

**Support:**

**Please choose your academic program:**
MD

**What year are you in the program?**
2

**Body of Abstract (300 words or less)**

**ABSTRACT**

**BACKGROUND**

Chronic diseases like diabetes and hypertension cause high levels of morbidity and mortality. Homebound patients with chronic diseases may face barriers to reaching clinical goals of care because of difficulty accessing primary care. The perceptions of homebound patients and their caregivers about the barriers they face in managing their chronic diseases are unknown.

**OBJECTIVES**

Objective 1: To determine the effects of homebound primary care on both the utilization and type of hospitalizations by homebound patients with chronic disease.

Objective 2:

**METHODS/PROCEDURES**

A cross sectional-survey of homebound patients and their caregivers with hypertension, diabetes, or both, of a large academic primary care practice. The exact patient selection process and questionnaire are not yet developed. The study will compare hospitalization data of homebound patients both in the HCP and on the waitlist in order to determine if homebound patients with homebound primary care are less likely to have...
avoidable hospitalizations, thus making the house call program effective.

SIGNIFICANCE

An improved understanding of the utilization of care and hospitalizations by homebound patients in achieving chronic disease care goals, may provide insight into how to better address the primary care needs of this population. This information may help policymakers and public health officials decide on best models of care for chronic diseases in the homebound.
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Heterotopic Ossification in Combat-Related Traumatic Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>ENS Scott C. Wagner, USNR</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>ENS Kevin Wilson, USNR; Dr. Michael Ring, NIH; CDR Eric Elster, MD</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>CDR Eric Elster, MD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Surgery, Orthopedic Surgery</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>National Naval Medical Center, Bethesda, MD</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Despite its significance as a problematic clinical entity, few studies have attempted to characterize the epidemiology and risk factors for the development of heterotopic ossification in patients suffering major traumatic injuries. Given the drastic increase in traumatic injuries seen in military service-members since the onset of Operation Iraqi Freedom in 2003, the purpose of this study was to report the incidence of and risk factors for the development of heterotopic ossification in patients suffering from major combat-related traumatic injuries. We identified 1,213 inpatients with at least one traumatic injury sustained as part of either Operation Enduring Freedom or Operation Iraqi Freedom, who had been managed at the National Naval Medical Center, between the dates of March 1st, 2003 and December 31st, 2006. We examined radiographic reports of all patients for evidence of heterotopic ossification; the mechanism and area of injury, internal or external orthopedic fixation, amputation and other risk factors were examined for all patients whose records showed development of heterotopic ossification. Of 1,213 in-patients with at least one traumatic injury sustained as part of either Operation Enduring Freedom or Operation Iraqi Freedom, who had been managed at the National Naval Medical Center, between the dates of March 1st, 2003 and December 31, 2006. 102 patients (70%) developing HO had injuries sustained via a blast mechanism. 73 patients (50%) were treated with open reduction, internal fixation at the site of future HO development. 58 patients (40%) developed HO after an amputation of an injured limb. 44 patients (30%) had multiple HO sites. 30 patients (20%) treated with external fixation developed HO at the site. Characterization of this problem is currently being continued at the National Naval Medical Center. However, it is clear that the incidence of heterotopic ossification is increased in patients suffering from traumatic blast injuries, and protocols for prophylaxis against HO may be refined with these data as a guide.</td>
</tr>
<tr>
<td>1. Title</td>
<td>Propofol-Induced Production of Nitric Oxide and Nitrosylation of PKC-(epsilon) in Diabetic Cardiomyocytes</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Hollis Walker</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Peter J. Wickley, B.S., Brad A. Martin, B.S., Paul A. Murray, Ph.D, Derek S. Damron, Ph.D.</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Derek Damron</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Center for Anesthesiology Research</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Cleveland Clinic Foundation</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | Background: Diabetes-induced cardiac dysfunction is characterized by a decrease in myocardial performance independent of vascular disease. Our lab has demonstrated that 1) nitric oxide synthase (NOS) and protein kinase C (PKC) isoforms are up-regulated and 2) propofol decreases myofilament Ca2+ sensitivity via a PKC-NOS-dependent pathway in diabetic cardiomyocytes. Moreover, nitric oxide (NO) nitrosylates tyrosine residues on PKC-E, facilitating its translocation from cytosolic to membrane fractions. Our study determined whether propofol stimulates NO production and subsequent nitrosylation of PKC-E in diabetic cardiomyocytes. 

Methods: Cardiomyocytes were obtained from normal and streptozotocin-induced diabetic rat hearts. NO production was assessed with and without propofol, S-Nitroso-N-acetylpenicillamine (SNAP), and phorbol myristate acetate (PMA) using an ELISA kit. Pretreatment with bisindolylmaleimide I (BIS) was used to assess the role of PKC in NO production. Immunoblots of whole cell lysates following exposure to SNAP and propofol with and without L-NAME and Ebselen assessed tyrosine nitrosylation of PKC-E and the subcellular distribution and translocation of PKC-E.

Results: In diabetic hearts, propofol, SNAP and PMA increased NO production by 74+10%, 128+12% and 85+4%, respectively, compared to control. PKC inhibition by BIS attenuated the propofol-induced increase in NO production by 41+11%. Propofol, SNAP and PMA increased nitrosylation of immunoprecipitated PKC-E 118+13%, 201+19%, and 143+11%, respectively. The propofol-induced increase in nitrosylation was attenuated by the NOS inhibitor, L-NAME (89+12%) and the peroxynitrite scavenger, Ebselen (96+9%). PKC-E was primarily in the cytosolic fraction (81+12% of total protein content). Propofol and SNAP
caused an increased translocation from 19+9% in controls to 71+17% and 43+13%, respectively, which was attenuated by L-NAME (54+14%) and Ebselen (53+17%).

Discussion: Propofol causes a PKC-dependent increase in NO production in diabetic cardiomyocytes. This increase could be partially responsible for the depressed contractile function observed in diabetic hearts. Propofol also increased tyrosine nitrosylation of PKC-E, which contributed to the translocation of PKC-E to the membrane. This nitrosylation potentiates the propofol-induced activation of PKC in diabetic hearts.

11. What was your role in this project? Experimenter

1. Title The treatment of Multiple Sclerosis with Lisonipril peptide derivatives

2. Student Presenter: Hollis Walker

3. Co-workers and Collaborators: Peggy Ho, PhD

4. Advisor: Dr. Lawrence Steinman

5. Departments: Neurology

6. Institutions: Stanford University School of Medicine

7. Support:

8. Please choose your academic program: MD

9. What year are you in the program? 2

10. Body of Abstract (300 words or less) Background: It had previously been shown that some naturally occurring peptides, with concentrations that increased in the presence of an ACE inhibitor, can actually reverse inflammation in rats with experimentally induced colitis and those with heart failure after myocardial infarction.

Hypothesis: Can small peptide derivatives of Lisinopril, an angiotensin-converting enzyme inhibitor, but used to treat an inflammatory neurological disease like Multiple Sclerosis.

Methods: 50 female SJL-strain mice were induced with PLP 139-1514, a peptide used that would produce EAE (an animal model of multiple sclerosis), and then subsequently treated with one of the 5 possible treatment options. The options included PBS (control group), Lisinopril,
Ac-SDKP, MIF, Tuftsin.

Results: The in vivo data collected showed some indication that mice treated with MIF and Ac-SDKP helped to prevent the onset and severity of disease.

Conclusions: This preliminary data looks very promising in showing that certain peptide derivatives can reduce the inflammatory processes seen in an animal model of Multiple Sclerosis.
DNA in cells is found in chromatin, the combination of DNA and histone proteins that condenses long DNA molecules into a small nucleus. Chromatin remodeling complexes contain ATP-dependent enzymes that essentially slide histone proteins along the DNA to allow or restrict access to specific DNA sequences. Some nuclear protein complexes contain both histone modification and chromatin remodeling capabilities such as the NURD (nucleosome remodeling and deacetylation) complex. Within the NURD complex is the chromodomain helicase DNA binding protein 4 (CHD4), also known as Mi-2beta. Antibodies to the CHD4 protein known as anti-Mi-2 autoantibodies are commonly found in some patients with skin and muscle disorders such as dermatomyositis, polymyositis, and inclusion body myositis. In addition, CHD4 has been shown to play a role in regeneration of the lens of the eye.

We investigated the role CHD4 during eye development by performing gene silencing techniques specific for the CHD4 gene. We injected small amounts of antisense morpholino oligonucleotides into the cytoplasm of Xenopus laevis embryos in order to inhibit translation of the CHD4 protein, and then monitored the development of the resulting CHD4 morphants. Injection of 43 ng of CHD4 antisense morpholino resulted in obvious and severe ocular malformations, a pronounced groove in the forehead between the eyes and cement gland, a noticeably shortened anterior-posterior length, and lack of response upon stimulation. Surprising, injection of 86 ng of CHD4 morpholino did not yield the same level or spectrum of phenotypes, but that may be attributed to the low sample size. Embryos injected with the same amounts of CHD4 inverse morpholino or sterile nanopure water were used as controls along with uninjected embryos, all of which developed normally in these experiments. In summary, it is clear that CHD4 plays an essential role in early
development, and the specific activities of CHD4 in the early embryo will be the subject of future studies.

<p>| 11. What was your role in this project? | Researcher |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Title</td>
<td>Cytotoxicity of Bispecific Antibody Gastrin Releasing Peptide Receptor antagonist/anti-CD3 (antag2/OKT3)</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Allen S. Wang</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td></td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Jie-hua Zhou, Edward D. Ball</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Medicine and Moores University of California, San Diego Cancer Center</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>University of California, San Diego</td>
</tr>
<tr>
<td>7. Support:</td>
<td>related disease research program</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
</tbody>
</table>
| 10. Body of Abstract (300 words or less) | 1. Background: Currently, there is development of bispecific antibodies targeting proteins expressed by neoplasms and simultaneously targeting immune cells of the body. By binding to both the neoplasm as well as leukocytes, a more specific and effective elimination of the cancer can occur. OKT3 is a murine monoclonal IgG2a antibody that binds to CD3 on the membrane of T cells and activates the T-cell. Gastrin releasing peptide receptor (GRP-R) antagonist(Antag2)/antiCD3(OKT3) bispecific antibody molecule has been designed and has been studied in the targeting of small cell lung cancer by targeting GRP-R expressing tumors and recruiting T-cells.

2. Hypothesis: I believe that by using the Antag2xOKT3 antibody, there will be an increase in lymphocyte and monocyte activation, and increased cytotoxicity of tumor cells relative to no treatment and anti-Her2/anti-CD64.

3. Method: The breast tumor cells cultured were T47D cells which express GRP-R and SKBR3 cells with significantly less GRP-R expression. By using Lactose Dehydrogenase assays to monitor cell lysis, cultured and isolated lymphocytes are armed with either OKT3xAntag2 antibody or with anti-Her2/antiCD64 antibody or with nothing and applied to tumor culture. Conditions regarding tumor population, dose concentration of antibody, lymphocyte population were tested to optimize experimental results.

4. Results: The overall results demonstrated a significant(>2SD) increase in tumor cell lysis relative to treatment with anti-Her2/antiCD64. Between the two different cell lines the T47D had a more drastic increase in tumor cell lysis compared to the SKBR3 cell line.

5. Conclusion: Although further testing of alternative conditions and an efficient cytogenetic method of testing cell lysis and apoptosis is needed, initial LDH assay tests demonstrate a promising increase in cytotoxicity |
specifically for Gastrin Releasing Peptide Receptor expressing cells. This is seen in the different degrees of cell lysis between the two tumor cell lines treated with similar conditions. Furthermore, a significant increase in cell lysis by the OKT3xAntag2 antibody versus the anti-Her2/antiCD64 antibody shows potential for future breast tumor treatment.

| 11. What was your role in this project? | Student Researcher |
**Body of Abstract (300 words or less)**

Diffusion tensor imaging (DTI) is a relatively new magnetic resonance technique that allows white matter bundles in the brain to be identifiable in vivo. Combined with fiber tractography technique, DTI has been proposed as a preoperative planning protocol for brain tumor resections as well as a diagnostic tool for brain abnormalities. However, current limited understanding of DTI has minimized its translation into clinical practice. The aim of this study is to develop a normal anatomy atlas of the major white matter bundles and to demonstrate the variability of the white matter tractography to changes in the fractional anisotropy (FA) setting and angle of deflection (AOD) setting. Diffusion images with 12-direction encoding of both control subjects and brain tumor patients were processed and generated. White matter tractography was performed using a tensor deflection algorithm, in which the FA and AOD thresholds were varied, while step length and number of samples per voxel length were held constant. Individual regions of interest (ROIs) were regenerated in three dimensions and in three planes from a single seed point for multiple iterations of FA and AOD values. Tractographies of corticospinal tract, internal capsule, cingulum, and corpus callosum were obtained and illustrated. Threshold values of FA and AOD showed to have a significant impact on the number of fiber tracts and the boundaries of the fibers. Although the number of fiber tracts was increased by a decrease in FA threshold or an increase in AOD threshold, it reached maximum and stayed constant when FA threshold was less than 0.20, or when AOD threshold was greater than 20 degrees. Additionally, the contour of a tumor was better defined at a lower FA threshold, where the amount of aberrant fibers was also increased. Future studies should be focused on the appropriateness of fiber tracts and their clinical correlations. Further streamlined DTI and tractography software and a high-capacity
workstation are highly recommended.
## Background

In congenital long QT syndrome type 1 (LQT1), episodes of ventricular tachycardia are usually triggered by exercise and can be prevented in most patients by beta-blocker therapy. In addition, LQT1 associated with a normal resting QT interval can be unmasked by the abnormal QT response to exercise testing (failure of the QT interval to shorten normally). Preliminary data from our laboratory show that the exercise QT intervals of patients with LQT1 are partially normalized by beta-blocker therapy. It is currently unknown if beta-blockers modify the QT/heart rate relationship (a primary effect on repolarization) or if the "normalizing" effect is due to the inability of subjects on beta-blockers to attain sufficiently high workloads (due to reduced heart rate) for prolongation to occur. Moreover, the physiologic response of the exercise QT interval to beta-blockers in healthy control subjects is not well-described.

## Objective

The objective of this study is to define the impact of beta-blocker therapy on the QT response to exercise and recovery in normal subjects.

## Methods

Approximately 36 healthy adult subjects age-matched to previously studied LQT1 subjects will undergo 1) screening history, 2) two weeks of beta-blocker therapy ending in an exercise test, and 3) two weeks of placebo therapy ending in an exercise test. Beta-blocker and placebo will be administered randomly in a double-blind fashion. The QT response to exercise and recovery will be compared between drug-free and beta-blocker-treated states. These data will be compared to those previously collected for LQT1 subjects.

## Results

To date, eight subjects have completed both phases of the exercise testing. Enrollment is currently ongoing, and preliminary data analysis to confirm the quality of data has also begun. Final data analysis, including comparison with LQT1 subjects, cannot commence until all

<table>
<thead>
<tr>
<th>1. Title</th>
<th>QTc in Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Gregory Ward</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Elizabeth Kaufman, MD; Mary Dettmer, RN; Jennifer Ball</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Elizabeth Kaufman, MD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>MetroHealth Heart and Vascular Center</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>MetroHealth Hospital</td>
</tr>
<tr>
<td>7. Support:</td>
<td>MetroHealth Heart and Vascular Center; NHLBI Summer Research Grant</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Background. In congenital long QT syndrome type 1 (LQT1), episodes of ventricular tachycardia are usually triggered by exercise and can be prevented in most patients by beta-blocker therapy. In addition, LQT1 associated with a normal resting QT interval can be unmasked by the abnormal QT response to exercise testing (failure of the QT interval to shorten normally). Preliminary data from our laboratory show that the exercise QT intervals of patients with LQT1 are partially normalized by beta-blocker therapy. It is currently unknown if beta-blockers modify the QT/heart rate relationship (a primary effect on repolarization) or if the &quot;normalizing&quot; effect is due to the inability of subjects on beta-blockers to attain sufficiently high workloads (due to reduced heart rate) for prolongation to occur. Moreover, the physiologic response of the exercise QT interval to beta-blockers in healthy control subjects is not well-described. Objective. The objective of this study is to define the impact of beta-blocker therapy on the QT response to exercise and recovery in normal subjects. Methods. Approximately 36 healthy adult subjects age-matched to previously studied LQT1 subjects will undergo 1) screening history, 2) two weeks of beta-blocker therapy ending in an exercise test, and 3) two weeks of placebo therapy ending in an exercise test. Beta-blocker and placebo will be administered randomly in a double-blind fashion. The QT response to exercise and recovery will be compared between drug-free and beta-blocker-treated states. These data will be compared to those previously collected for LQT1 subjects. Results. To date, eight subjects have completed both phases of the exercise testing. Enrollment is currently ongoing, and preliminary data analysis to confirm the quality of data has also begun. Final data analysis, including comparison with LQT1 subjects, cannot commence until all</td>
</tr>
</tbody>
</table>
healthy subjects have completed the trial (due to the double-blind nature of the study).

| 11. What was your role in this project? | Research Design and Recruitment |
1. Title | Estimating doxorubicin transport properties to improve intratumoral drug delivery

2. Student Presenter: | Brent D. Weinberg


4. Advisor: | Agata A. Exner

5. Departments: | Department of Biomedical Engineering (Weinberg, Patel, Saidel)  
Simmons Comprehensive Cancer Center (Gao)  
Department of Radiology (Exner)

6. Institutions: | Case Western Reserve University (Weinberg, Patel, Saidel, Exner)  
University of Texas-Southwestern Medical Center (Gao)

7. Support: | Department of Defense Breast Cancer Research Program Predoctoral Fellowship

8. Please choose your academic program: | MD PHD

9. What year are you in the program? | 6

10. Body of Abstract (300 words or less) | Developing an intratumoral drug delivery implant to supplement radiofrequency (RF) ablation requires detailed knowledge of the drug transport properties in tumor tissue. To gain insight into tissue properties governing drug release from these implants and local drug transport, a one-dimensional (1-D), radially-symmetric finite element method (FEM) drug transport model was generated. The model was based on previous work where doxorubicin distribution from implants was measured on days 4 and 8 in non-ablated and ablated rabbit VX2 liver carcinomas. In this model, the implant occupied the center, and was surrounded by non-ablated or ablated tumor and normal liver. Transport was governed by two parameters in each tissue: diffusion, D, and elimination, G. Values for D and G were estimated by coupling the FEM solution with least squares optimization to minimize the sum of square residuals between the model output and experimental data. In non-ablated tumor, D was estimated at $5.0 \times 10^{-11} \text{ m}^2\text{s}^{-1}$ (25% slower than normal liver), and G was $5.9 \times 10^{-5} \text{ s}^{-1}$ (94% slower than normal liver). In ablated tumor, diffusion varied as a function of distance from the ablation center. Doxorubicin diffusion near the center was $10.6 \times 10^{-11} \text{ m}^2\text{s}^{-1}$, but in the periphery of ablation it decreased to levels seen in normal liver. In contrast, the elimination rate was homogeneous throughout the ablated tumor but varied as a function of time. Before day 4, G was near 0 and increased linearly between days 4 and 8 to $5.7 \times 10^{-5} \text{ s}^{-1}$, a value similar to that of non-ablated tumor. By fostering doxorubicin distribution and reducing elimination, RF ablation opens a window of time in which local drug distribution around an intratumoral implant will be improved.
Knowledge of these tissue properties can be used to design better treatments that maximize drug delivery to tumor areas which are most at risk for recurrence.

11. What was your role in this project?

Doctoral student performing thesis research

1. Title

Liver tumor treatment with combined radiofrequency ablation and doxorubicin-containing polymer implants

2. Student Presenter:

Brent D. Weinberg

3. Co-workers and Collaborators:

Elvin Blanco, Scott Lempka, James Anderson, Jinming Gao

4. Advisor:

Agata Exner

5. Departments:

Biomedical Engineering (Weinberg, Lempka)
Institute of Pathology (Anderson)
Simmons Comprehensive Cancer Center (Blanco, Gao)
Department of Radiology (Exner)

6. Institutions:

Case Western Reserve University (Weinberg, Lempka, Anderson)
University of Texas-Southwestern Medical Center (Blanco, Gao)
University Hospitals of Cleveland (Exner)

7. Support:

Department of Defense Predoctoral Fellowship BC043453

8. Please choose your academic program:

MD PHD

9. What year are you in the program?

5

10. Body of Abstract (300 words or less)

Radiofrequency (RF) ablation has been developed as a minimally-invasive treatment for refractory liver cancer. However, treatment efficacy is limited by frequent tumor recurrence around the ablation boundary. To improve the therapeutic outcome of the treatment, we have developed biodegradable polymer implants (millirods) that can be placed directly into tumors to release chemotherapeutic agents. Cylindrical implants releasing their drug contents over 24 hours were fabricated using 60% poly(D,L-lactide-co-glycolide) (PLGA), 26.5% NaCl, and 13.5% doxorubicin. To test local drug distribution and treatment efficacy of these implants, we treated VX2 liver tumors (11 mm diameter) in rabbits with RF ablation insufficient to treat the entire tumor (8 mm treatment diameter). Following the ablation, drug-free or doxorubicin-containing implants were placed in the tumor center. Tumors were removed 4 or 8 days after millirod implantation, and treatment efficacy was assessed using tumor size, histology, and fluorescence measurement of drug distribution. Tumors in both test groups recurred around the boundary of the RF
ablated region. High doxorubicin concentrations were found within the ablation region at both 4 and 8 days, but the concentrations declined rapidly at the boundary between normal and ablated tissue. This region was characterized by a thick inflammatory layer with extensive collagen deposition, which appeared to restrict drug transport out of the ablated zone and limit drug spread to viable tumor tissue. Although the outcome of the combined treatment did not offer significant improvement over ablation alone, the extensive drug distribution in the ablated tissue shows promise for future investigation into the approach.
Developing a Rodent Model for Human Vascular Cognitive Impairment

Katherine Williams

Dr. Alison Hall, Dr. Warren Selman

Dr. Robert Miller

Neurosciences, Neurosurgery

Case Western Reserve University
University Hospitals Case Medical Center

NIH T-35 Fellowship

MD MS

2

Cerebrovascular disease is recognized as a common cause of cognitive disease and dementia in later life. Cellular and molecular changes accompanying this diagnosis are not understood. Proper animal models in which potential therapies may be tested are not yet available.

Microsphere embolism in rodent brains using 900 large (50 um) beads can produce sustained multiple infarct areas on several brain areas, resulting in areas with reduced perfusion and varying degrees of collateral flow. Associated neural damage produces learning and memory impairments. We hypothesized that more subtle and diffuse infarction or "mini-strokes" could elicit reproducible, measurable molecular and histological changes corresponding to human VCI, including increased gliosis, modest neuronal loss, and formation of lacunae in white matter.

Fourteen adult male and female rats underwent surgery over the course of four weeks. 100, 200, or 400 microspheres were injected into the left internal carotid artery through a 27G ½ needle inserted into the left common carotid artery.

Histological changes were assayed at 2.5 weeks post-surgery. Initial results derived from animals injected with 100 microspheres showed increased expression of myelin basic protein in brain regions supplied by the injected artery. However, no changes in glial fibrillary acidic protein (GFAP) expression were apparent. Lacunae and significant neuronal loss were not observed. Further studies are needed to determine the significance of these results, as well as to examine changes that occur with higher doses of microspheres, with multiple injections performed on different occasions, and with longer time periods between surgery and
histological analysis. Neurobehavioral analyses are also needed to examine changes in learning and memory. This will help to determine which combination of these factors, if any, may serve as an appropriate animal model in which potential therapies for VCI may be investigated.

| 11. What was your role in this project? | Development of surgical design, performance of surgeries, and histological analysis. |
OBJECTIVE: To explore the effect of physician religiosity on delivery of end-of-life care.

INTRODUCTION: The impact of religion and religiosity in medicine has proven difficult to quantify. However, studies have shown increased patient satisfaction when patients and physicians are matched on personal and interpersonal characteristics. Research has also demonstrated the effects of physician psychological characteristics on performance. Physician and patient health information processing styles (HIPS; e.g. monitoring or blunting) affect how much information physicians provide to patients and how much information patients want from their physicians.

METHODS: Subjects included oncology attending physicians, fellows and an oncology nurse from a public urban tertiary care hospital or an urban Veteran’s Affairs hospital who agreed to participate in the study. Subject responses were gathered from a baseline interview conducted as part of a larger study on the effect of a counseling and decision support intervention for recently diagnosed late-stage cancer patients. Interviews were conducted in person by trained personnel using a survey containing both validated and newly designed measurement tools. Physician religiosity was measured on a 5-point scale and compared with physician demographics, perceptions, attitudes toward end-of-life care, response to uncertainty, and HIPS to identify correlations.

RESULTS: Physician religiosity was negatively correlated with both doctors’ predictions of the percentage of patients who would choose palliative care at the time of diagnosis of stage IV cancer and with the degree of physicians’ monitoring HIPS (both \( r = -0.4, p < 0.05 \)).

CONCLUSIONS: Our findings suggest that oncology health professionals who were more religious believe that fewer of their stage IV patients would choose palliative care and are less likely to seek out information regarding
Their own health stressors. These characteristics may affect health care delivery, patient and family satisfaction with their health care, and utilization of health services.

<p>| 11. What was your role in this project? | Research Assistant |</p>
<table>
<thead>
<tr>
<th>1. Title</th>
<th>Effect of Downregulation of NHERF1 on RACK1 Surface Expression in Polarized Epithelial Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Nicholas Wilson</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Laura Smith, Xiangyun Wang, Dr. Andrew Resnick</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Carole Liedtke</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Division of Pediatric Pulmonary</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University School of Medicine</td>
</tr>
<tr>
<td>7. Support:</td>
<td>NIH T32 Grant</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Cystic Fibrosis (CF) is a genetic disease that affects multiple organ systems and confers significant morbidity and mortality. The ?F508 mutation, a class II mutation that results in a misfolded, prematurely-degraded chloride channel, accounts for 90% of CF. A small amount of mutated protein evades degradation to reach the cell’s apical surface where it is a functional chloride channel, but suffers a drastically shortened half-life. RACK1 is a scaffold protein at the core of a larger proteome that is colocalized with CFTR on the apical membrane, and is believed to be important for CFTR residence in the membrane. NHERF1 proteins within this proteome bind RACK1, cytoskeletal tubulin, and CFTR, and may be necessary for the stability of RACK1 and CFTR in the apical membrane. Understanding the role of NHERF1 within the RACK1 proteome and the processes affecting the tenure of ?F508 CFTR in the apical membrane could have therapeutic implications. To approach this question we used siNHERF1 on Calu-3 cells in culture, which are an immortal line of lung adenocarcinoma cells with abundant expression of CFTR. Several rounds of optimization for siNHERF1 in the Calu-3 cells concluded that a significant knockdown of NHERF1 (84.79% loss) could be achieved through electroporation of SMARTpool siNHERF1 from Dharmacon 48 hours before protein collection. The cells were concurrently transfected with GFP, and GFP expression was recorded with fluorescent microscopy to document successful transfection, while the knockdown was confirmed by western blot analysis. Transfected cells were labeled apically with biotin, lysed, and incubated with strepavidin beads to immunoprecipitate the biotinylated apical proteins. The proteins were separated from the beads and a western blot was performed. Initial evidence indicates that there may be a decrease in the levels of RACK1, although more data is needed to support this finding.</td>
</tr>
</tbody>
</table>


| 11. What was your role in this project? | Student Researcher |
1. **Title**
   Retrospective Chart Review of Primary Central Nervous System Lymphoma (PCNSL) Treated with Methotrexate Monotherapy (HDMTX)

2. **Student Presenter:**
   Nina Woldenberg

3. **Co-workers and Collaborators:**
   Julien Cobert

4. **Advisor:**
   Dr. Fred H. Hochberg

5. **Departments:**
   Neurology

6. **Institutions:**
   The Massachusetts General Hospital

7. **Support:**
   The Crile Foundation

8. **Please choose your academic program:**
   MD

9. **What year are you in the program?**
   2

10. **Body of Abstract (300 words or less)**

    PCNSL represents one of the few potentially curable malignant brain tumors. Untreated, median survival is 1.5 months. This can be improved to over 4 years with multi-drug therapies to which radiation of the brain is commonly added. Whether therapies based on HDMTX are more efficacious than HDMTX alone continues to be problematic, as well as how these therapies add to response and quality of life. This review, the largest performed to date, is of 117 consecutive immunocompetent patients with diagnosed PCNSL treated at the Massachusetts General Hospital from January 1, 1980 to August 1, 2007.

    HDMTX (8 g/m2 or 3.5 g/m2) absent radiation therapy produced complete response in 68 (58%) of patients by the (median) 6th cycle of therapy; partial response (PR) in 35%, while 8 patients (~ 7%) progressed on therapy (PD). Despite an initial partial response 27 of 41 patients (23%) eventually progressed. Thirty-nine of the 68 CR patients (57%) ultimately recurred over a median interval of 15.5 months. Almost half of these recurrences appeared (49%) despite ‘maintenance’ of HDMTX therapy every four months. The ‘maintenance’ therapy appeared to have prolonged the progression free survival.

    Survival calculations for the 117- member cohort revealed median survival of 30 months (0 – 157 months) in comparison to CR patients (N=68) who had a progression free survival of 28 months (0 – 157 months) and overall survival of 48 months (0 – 152 months). These survivorships compare favorably to those reported with HDMTX-based therapies in the literature.

    I conclude that HDMTX is efficacious for approximately one-half of PCNSL recipients but hypothesize that MTX – enzyme transport, or reduced folate
carrier status may be responsible for lack of benefit experienced by patients with identical demographic and pathologic features of PCNSL.

| 11. What was your role in this project? | Created inclusion and exclusion criteria, Excel spreadsheet, reviewed pertinent literature and records on one-half of patients to formulate a durable review of Methotrexate Monotherapy from 1980 to 2007 at Massachusetts General Hospital. |
## WOOLRIDGE, STEFANIE

<table>
<thead>
<tr>
<th>1. Title</th>
<th>Evaluation of laboratory quality improvement program for sputum smear microscopy in Kampala, Uganda.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Student Presenter:</td>
<td>Stefanie Woolridge</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Deus Lukoye, Nicholas Ezati</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Achilles Katamba, Christopher Whalen</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Epidemiology and Biostatistics</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>CWRU</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD MPH</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>BACKGROUND: Well functioning laboratories are required for the successful management of tuberculosis. Without accurate detection of cases through sputum smear microscopy, the efficacy of all standardized treatment and prevention programs are compromised. OBJECTIVE: To assess the outcomes of a laboratory quality improvement program. METHOD: A standardized on-site quality assessment survey was conducted at fifteen tuberculosis diagnostic laboratories in Kampala in 2002 and in again in 2005 after implementation of targeted interventions based on the 2002 survey. The targeted interventions included skills and knowledge training, implementation of regular support supervision, and provision of supplies through a revamped centralized system. Results of the surveys were compared between 2002 and 2005. RESULTS: A marked improvement in almost all categories of laboratory performance was observed; particularly in supply provision, record keeping, external quality control measures, and worker knowledge and motivation. CONCLUSION: Targeted interventions implemented in response to periodic standardized quality assessment surveys are an important step forward in improving the performance of diagnostic microscopy laboratories in Kampala, Uganda.</td>
</tr>
</tbody>
</table>
### 1. Title
Impact of Obesity on the Severity and Therapeutic Responsiveness of Acute Episodes of Asthma

### 2. Student Presenter:
Karen H. Yeh

### 3. Co-workers and Collaborators:
Mary E. Skowronski, Albert J. Coreno, Gayle Galan, Frank J. Kaeberlein, Roy E. Seitz, Karen D. Villaba, and Howard Dickey-White

### 4. Advisor:
E. R. McFadden, Jr.

### 5. Departments:
Division of Pulmonary, Critical Care, and Sleep Medicine and Department of Medicine

### 6. Institutions:
MetroHealth Medical Center; University Hospitals Case Medical Center; and Center for Academic Clinical Research and the General Clinical Research Center of Case Western Reserve University School of Medicine

### 7. Support:
Grants HL33791 and HL04140 from the National Heart, Lung, and Blood Institute and by General Clinical Research Grant M01 RR00080 from the National Center for Research Resources, U.S. Public Health Services

### 8. Please choose your academic program:
MD

### 9. What year are you in the program?
2

### 10. Body of Abstract (300 words or less)
It has been suggested that obesity adversely influences both the severity and therapeutic responsiveness of chronic asthma. However, it is unknown whether such events play a role in acute disease. The objective of this study was to determine the impact of obesity on the presenting signs, symptoms, and pulmonary function of acutely ill patients with asthma, as well as the effect of routine treatment. We compared clinical features, airflow limitation, and albuterol effectiveness in 90 obese and 100 non-obese asthmatics as they came to emergency departments in a university hospital system. The patients were sequentially selected from a database based upon their dates of presentation. Assessments and treatments were standardized across institutions using a care path, and admission and discharge decisions were made according to predetermined criteria. The intensity of airflow limitation was measured by peak expiratory flow rates. The obese subjects had a body mass index of 37.4 ± 0.9 kg/m² compared to 25.0 ± 0.3 in the non-obese (p < 0.001). There were no differences in signs or symptoms between groups. However, the obese individuals had a higher oxygen saturation as measured by pulse oximetry (96.6 ± 0.3 % versus 95.7 ± 0.3, p = 0.05) and peak flow (40.4 ± 2.0 percent predicted versus 33.7 ± 1.7, p = 0.01). Each group responded similarly to albuterol, and there were no differences in admission/discharge ratios. Our data indicate that obesity, per se, does not adversely influence acute episodes of asthma. In fact, obese patients tend to present with less airflow limitation and better oxygen saturations, suggesting that the combination of obesity and
<p>| 11. What was your role in this project? | Performance of study; Collection, analysis, and interpretation of data |</p>
<table>
<thead>
<tr>
<th><strong>1. Title</strong></th>
<th>Colon Cancer Secreted Protein-1 (CCSP-1) expression by leukocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2. Student Presenter:</strong></td>
<td>Yu Zhang</td>
</tr>
<tr>
<td><strong>3. Co-workers and Collaborators:</strong></td>
<td>Stephen Fink, Ph.D.</td>
</tr>
<tr>
<td><strong>4. Advisor:</strong></td>
<td>Sandy Markowitz, M.D., Ph.D.</td>
</tr>
<tr>
<td><strong>5. Departments:</strong></td>
<td>Medicine</td>
</tr>
<tr>
<td><strong>6. Institutions:</strong></td>
<td>Case Western Reserve University, Cleveland, OH 44106</td>
</tr>
<tr>
<td><strong>7. Support:</strong></td>
<td></td>
</tr>
<tr>
<td><strong>8. Please choose your academic program:</strong></td>
<td>MD</td>
</tr>
<tr>
<td><strong>9. What year are you in the program?</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>10. Body of Abstract (300 words or less)</strong></td>
<td>Cancers of the colon and rectum are the second leading cause of cancer incidence and death among adult Americans. The Markowitz lab has previously identified a novel 158 kDa colon cancer secreted protein -1 (CCSP-1), whose transcript expression is generally absent in normal colon, but is induced an average of 50 -fold in colon cancers, adenomas, and cell lines. In a multi-tissue northern blot study, CCSP-1 was also found to be expressed in the lymph nodes, tonsils, brain, placenta, and in the lungs. CCSP-1 expression in tonsils was validated by real time PCR and by western blot. The presence of CCSP-1 in immune privileged tissues suggests a possible immunoregulatory role of CCSP-1. Using dual labeling immunohistochemistry, CCSP-1 positive cells in the tonsils were determined to be positive for CD45, a marker for all leukocytes. To better understand the possible role of CCSP-1, we are currently attempting to identify the specific tonsillar immune cell that is making CCSP-1 by performing dual labeling IHC on tonsils in which we stain for CCSP-1 with respectively, CD3 as a marker for T cells, CD19 for B cells, CD138 for plasma cells, and CD68 for dendritic cells and macrophages.</td>
</tr>
<tr>
<td><strong>11. What was your role in this project?</strong></td>
<td>Experimental design, Performance of studies and/or experiments and Interpretation of data</td>
</tr>
<tr>
<td>1. Title</td>
<td>Neuronal Cell Cycle Reactivation in the Pathogenesis of Alzheimer’s Disease</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Shu-Han Zhu</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Hyoung-Gon Lee, Gemma Casadesus, Sandra Richardson, George Perry, Robert B. Peterson</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Dr. Mark Smith</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Department of Pathology, Department of Neurosciences</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Case Western Reserve University</td>
</tr>
<tr>
<td>7. Support:</td>
<td>Cell cycle inhibitors in Alzheimer Disease, 1R21AG031364-01</td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Although Alzheimer’s disease (AD) is marked by neuronal death, evidence shows that neurodegeneration is actually preceded by activation of many proteins related to cell cycle activity. To further elucidate the role of cell cycle activity in AD, we created a transgenic mouse with inducible MYC expression specific to the forebrain neurons (CaMKII-MYC). Upon induction, these mice developed changes similar to those seen in Alzheimer’s disease such as tau hyperphosphorylation, amyloid-beta accumulation, neural degeneration and cognitive decline. These results led us to test the capacity of roscovitine, a selective cyclin dependent kinase inhibitor (CDK) to prevent cell cycle activity and neurodegeneration. Roscovitine treated mice showed normal hippocampal histology and no neurodegeneration under hematoxylin and eosin stain whereas untreated mice showed evidences of neurodegeneration such as eosinophilic cytoplasm, shrunken cell bodies and nuclear condensation. Roscovitine also reduced the expression of cell cycle marker cyclin D1 in hippocampal neurons and reduced astrocytosis. Given the body of evidence supporting cell cycle disregulation as an early pathogenic factor in AD, cell cycle inhibitors may present a new preventative or therapeutic treatment for AD</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>My role included immunohistochemistry staining of mice brain sections and interpretation and presentation of results to Dr. Hyoung-gon Lee. After H&amp;E or immunohistochemistry staining, I interpreted the results blinded to the genetic status of the mouse sample. I did not know which slides come from control mice and which come from transgenic mice until after I record and present the results.</td>
</tr>
<tr>
<td>1. Title</td>
<td>Low Risk of Meperidine Induced Seizures in Children With Sickle Cell Disease</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>2. Student Presenter:</td>
<td>Gretchen Zsebik</td>
</tr>
<tr>
<td>3. Co-workers and Collaborators:</td>
<td>Mary Ann O'Riordan</td>
</tr>
<tr>
<td>4. Advisor:</td>
<td>Anthony Villella, MD</td>
</tr>
<tr>
<td>5. Departments:</td>
<td>Hematology/Oncology</td>
</tr>
<tr>
<td>6. Institutions:</td>
<td>Rainbow Babies and Children's Hospital</td>
</tr>
<tr>
<td>7. Support:</td>
<td></td>
</tr>
<tr>
<td>8. Please choose your academic program:</td>
<td>MD</td>
</tr>
<tr>
<td>9. What year are you in the program?</td>
<td>2</td>
</tr>
<tr>
<td>10. Body of Abstract (300 words or less)</td>
<td>Seizures are a potential serious side effect of meperidine caused by the production of toxic metabolites that require renal elimination. Consequently, meperidine is rarely used to treat pain at most pediatric medical centers. Over the past twelve years, Rainbow Babies &amp; Children's Hospital has utilized a pain protocol for sickle cell patients, administering meperidine or morphine every two hours at standard doses and weaning by 25% every 24 hours until the patients can be switched to oral analgesics. Our study compared the frequency of seizures among the pediatric sickle cell patients receiving meperidine and morphine over the last seven years to determine if the risk of meperidine induced seizures in this clinical setting is prohibitive. We performed a retrospective, observational study using billing codes to identify sickle cell patients who developed seizures while hospitalized for pain and the medications they were receiving at the time. A chart review was carried out to determine the cause of seizure and to eliminate patients with an underlying seizure disorder. 160 patients with diagnostic codes for sickle cell disease who were billed for either morphine or meperidine were identified over the course of 730 hospital admissions. Over the 730 admissions, the total morphine usage was 7388 hours versus 25,540 hours for meperidine. One seizure occurred with meperidine and one seizure occurred with morphine, but in the setting of eclampsia. The rate of seizures was 0.135 per 1000 hours of morphine exposure and 0.039 per 1000 hours of meperidine exposure. In conclusion, we observed an extremely low rate of seizures in pediatric sickle cell patients receiving meperidine, a rate comparable to that observed in those receiving morphine. In our experience, the risk of meperidine induced seizures was not prohibitive. Therefore, meperidine should remain a therapeutic option for pediatric sickle cell patients experiencing vaso-occlusive pain.</td>
</tr>
<tr>
<td>11. What was your role in this project?</td>
<td>I reviewed background literature, reviewed the data and charts, and I assisted with analysis and interpretation.</td>
</tr>
</tbody>
</table>