Washington University in St. Louis
SCHOOL OF MEDICINE

Sixth Annual

Research Training Symposium and Poster Session

October 17, 2011

Showcasing Basic, Clinical, and Translational research projects by junior faculty, fellows, residents, and training program students.

Washington University School of Medicine
Sixth Annual Research Training Symposium & Poster Session
October 17th, 2011
Farrell Learning and Teaching Center

12:45 – 1:00 pm Connor Auditorium
Welcome and Opening Remarks

Alison J. Whelan, MD
Professor of Medicine
Senior Associate Dean for Education

1:00 – 1:45 pm Connor Auditorium
Keynote Address

Jerry Menikoff, MD, JD
Director, Office for Human Research Protections
Office of Public Health and Science
Office of the Secretary, U.S. Department of Health and Human Services

1:45 – 3:00 pm Connor Auditorium
Oral Presentations

1:45 – 2:00 pm	Avraham Beigelman, MD
2:00 – 2:15 pm	Katherine Goetzinger, MD
2:15 – 2:30 pm	Steve Liao, MD
2:30 – 2:45 pm	Sumeeta Varma
2:45 – 3:00 pm	Allison Willis, MD

3:00 – 5:00 pm FLTC Atrium
Poster Session

This symposium is made possible by the Clinical Research Training Center (CRTC), a component of the Washington University Institute of Clinical and Translational Sciences (ICTS). The ICTS is part of a national consortium of medical research institutions, funded through the Clinical and Translational Science Awards (CTSA) that includes fifty-five medical research institutions in twenty-eight states and the District of Columbia, working together to improve the way biomedical research is conducted across the country. The consortium shares a common vision to reduce the time it takes for laboratory discoveries to become treatments for patients, and to engage communities in clinical research efforts. It is also fulfilling the critical need to train the next generation of clinical researchers. The CTSA initiative is led by the National Center for Research Resources (NCRR) at the National Institutes of Health. The CRTC is supported by NCRR Grant Numbers UL1RR024992, KL2RR024994, and TL1RR024995, Washington University in St. Louis School of Medicine, and Barnes-Jewish Hospital Foundation.

This symposium & poster session is co-sponsored by the Office of Medical Student Research, Washington University in St. Louis School of Medicine.

We gratefully acknowledge the support of Dr. Larry J. Shapiro, Executive Vice Chancellor for Medical Affairs and Dean, Washington University in St. Louis School of Medicine.

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Programs Represented

American Association of Neurological Surgeons (AANS)
The American Association of Neurological Surgeons (AANS) through the Neurosurgery Research and Education Foundation is offering the AANS Medical Student Summer Research Fellowship (MSSRF) program. The fellowship is open to medical students in the United States or Canada who have completed one or two years of medical school and wish to spend a summer working in a neurosurgical laboratory, mentored by a neurosurgical investigator who is a member of the AANS and will sponsor the student.
Website: http://aans.org

Center for Health Policy
The Washington University Center for Health Policy will sponsor summer opportunities for Washington University Medical Students between their first and second years. The purpose of these opportunities is to provide interested medical students with an in-depth exposure to major issues in health policy that explore the quality, organization and financing of health care in America. They may be undertaken within the health policy center or in organized health policy programs in government agencies, foundations and in other universities.
Program Director: William Peck, MD
Website: http://health policy.wustl.edu

Clinical Research Training Center (CRTC) KL2 Career Development Awards
The KL2 Career Development Awards Program at Washington University in St. Louis provides high-quality, multidisciplinary training in clinical and translational research to promote the career development of future clinical investigators. The program is aimed at fellows, post-doctoral scholars, and junior faculty committed to multidisciplinary clinical research. The program provides generous financial support and benefits that allow the scholar to focus on didactic studies and clinical research to further their career goals and to contribute to clinical and translational science. Trainees in the program have the opportunity to earn a Master of Science in Clinical Investigation (MSCI) degree or a Master of Science in Public Health (MSPH) degree from WU. Additionally, scholars participate in a hands-on, mentored, multidisciplinary research experience.
Program Director: Victoria Fraser, MD
Website: http://crtc.wustl.edu

Clinical Research Training Center (CRTC) Postdoctoral Program
The CRTC Postdoctoral Program is a training program designed for junior faculty, fellows, and postdocs with an MD, PhD, PharmD, or other doctoral degree in an allied health profession, who wish to pursue academic careers in clinical research. Scholars take six didactic courses in clinical investigation, conduct independent research under the tutelage of a mentorship committee, attend an ongoing seminar series to present and discuss research as a work-in-progress, and complete a final project - typically a submitted manuscript or grant application. There is also an option to earn a Master of Science in Clinical Investigation (MSCI) degree by taking additional elective coursework and research credits.
Program Director: Jane Garbutt, MBChB, FRCP, MHSc
Website: http://crtc.wustl.edu

Clinical Research Training Center (CRTC) Predoctoral Program
The CRTC Predoctoral Program is designed for students in medicine and allied health fields who wish to pursue academic careers in clinical research. Students engage in mentored clinical research and take courses on the design of clinical research and analysis of clinical research data. Students enrolled in the intensive research core also complete coursework in ethical and legal issues of clinical research, biostatistics, epidemiology, and scientific writing, and attend a journal club, conferences and special seminars. Intensive research trainees who successfully complete the coursework, attend the seminars, and prepare a manuscript for publication are eligible to receive the Masters in Science in Clinical Investigation (MSCI) degree.
Program Director: Jay Piccirillo, MD
Website: http://crtcpredoc.wustl.edu

David F. Silbert Summer Fellowship
In his memory, the David F. Silbert Summer Fellowship was set up to support short-term research internships for medical, graduate, or other students interested in his area of research. David's research focused on genetic biochemical and/or biophysical approaches to the study of specific membrane lipids in signal transduction pathways and in the assembly and function of eukaryotic cell membranes. Since his death from cancer in 1997, a number of biophysical techniques have been developed that address these issues. These techniques include, but are not limited to state-of-the-art fluorescence methods, structural determination using NMR or x-ray methods and computational approaches. All these techniques are directed towards understanding the role of macromolecular interactions in cellular function. It is now clear that membrane lipids and membrane proteins are functionally involved in all aspects of the regulation of cellular processes and that these processes must be studied at the level of macromolecular function.
Website: http://biochem.wustl.edu/silbertfellowship.html

Dean's Fellowship
This program is designed to provide medical students with a hands-on research experience. This can be a first-time experience or a project related or unrelated to research done as an undergraduate. Excellent mentors from a broad range of basic and clinical sciences are available. A Washington University Summer Research Fellowship can provide a strong background for application to the MA/MD and MD/PhD (MSTP) degree programs, can lead to abstracts at meetings and to publications, and can be important for applications for competitive residencies.
Program Director: Koong-Nah Chung, PhD

Forum for International Health and Tropical Medicine
The Forum for International Health and Tropical Medicine (FIHTM) brings together students and physicians at Washington University who are interested in international health. FIHTM aims to promote understanding of global health by enabling medical students to experience firsthand its locales, modes of delivery, disparities, and cultural manifestations. FIHTM organizes the Global Health Symposium each spring, as well as regular discussion lunch meetings with students and faculty. In addition, the group coordinates Spring Break community service trips for the first and second year medical classes. FIHTM offers financial and logistical assistance to students who wish to gain healthcare experience abroad and helps interested students find mentors within the university.
Program Director: Kathy Diemer, MD
Website: http://fihtm.wustl.edu

Fogarty International Clinical Research Scholars Program
The Fogarty International Clinical Research Scholars and Fellows (FICRS-F) Support Center at Vanderbilt offers a one-year clinical research training experience for graduate-level U.S. students in the health professions. This is an opportunity for highly motivated individuals to experience mentored research training at top-ranked NIH-funded research centers in developing countries. The FICRS program is designed primarily for students meeting all of the following qualifications: Each Fellowship is for a one year period. The term begins with an intensive orientation program on the NIH campus in Bethesda, MD in July. This is followed by approximately 10+ months of mentored clinical research training at the international site.
Website: http://www.fogartyscholars.org/scholars/international-clinical-research-scholars-program

Mallinckrodt Institute of Radiology Summer Research Program
The Mallinckrodt Institute of Radiology Summer Research Program offers undergraduate and medical students an excellent introduction to the following aspects of radiological sciences research: Magnetic Resonance Imaging, Magnetic Resonance Spectroscopy, Positron Emission Tomography, X-ray Computed Tomography, Contrast Agent Development, Digital Imaging, Optical Imaging, Diagnostic Radiology, Molecular Pharmacology, Nuclear Medicine, Radiopharmaceutical Development, Neuroscience Imaging, Cardiovascular Imaging, Optical Imaging, and Ultrasound.
Program Director: Suzanne Lapi, PhD
Website: http://www.mir.wustl.edu/education

MA/MD Program
Created in 1982, the Master's Degree Program allows medical students to participate in cutting-edge basic biomedical research or hypothesis-driven clinical research and earn a Master of Arts degree in preparation for a career in academic medicine. The program is highly flexible with an objective of providing students with an individualized research experience in an excellent environment. Scholars must be a full-time student in the first three years of the medical curriculum and in good standing without encumbrances at Washington University School of Medicine.
Program Director: Deborah Rubin, MD
Website: http://mamd.wustl.edu

Radiological Society of North America (RSNA)
The Radiological Society of North America Medical Student Grant has the purpose to increase the opportunities for medical students to have a research experience in medical imaging and to encourage them to consider academic radiology as an important option for their future. Recipients will gain experience in defining objectives, developing research skills and testing hypotheses before making their final choices for residency training programs.
Website: http://www.rsna.org/Foundation/ResearchMedicalStudentGrant.cfm

T32 NIH NHLBI Cardiovascular Biology Training Program
The Training Program in Cardiovascular Biology supports Predoctoral Students conducting Ph.D. thesis research and Postdoctoral Fellows in the early stages of post-graduate training. The goals of this Program are to provide outstanding research opportunities, well-rounded, multidisciplinary training in Modern Cardiovascular Biology, and mentoring to Predoctoral and Postdoctoral Trainees in the laboratories of one or more of the (22) participating faculty to prepare these individuals to be productive, independent scientists. The faculty derive from multiple (6) Departments (Biochemistry, Biomedical Engineering, Cell Biology and Physiology, Developmental Biology, Medicine and Radiology) and (4) Divisions (Cardiology, Chemistry, Endocrinology and Nutritional Science) within the Department of Internal Medicine, and include nationally and internationally recognized leaders in several areas of Modern Cardiovascular Biology including molecular biology, physiology, cell biology, biochemistry, modeling, imaging, pathology, genetics, and human cardiovascular disease mechanisms. The faculty are well-established, well-funded, experienced and highly productive investigators, and all are committed to providing the training, experience, resources, intellectual enthusiasm and mentoring needed to achieve the overall goals of the Training Program and to facilitate the professional development of the individual Program Trainees. In addition to research opportunities, trainees participate in weekly "Trainees in Cardiovascular Biology Series" and “Cardiovascular Research Seminar Series”. This Training Program is also actively involved in monitoring the progress and professional development and in the mentoring of Predoctoral and Postdoctoral Trainees.
Program Director: Jeanne Nerbonne, PhD

T32 NIH Otolaryngology Training Grant
This experience focuses on the student learning research concepts and techniques at the bench and bedside to become a scholarly physician, using as a model Sir William Osler. Four medical students may participate for three months (or less) of the summer. Monthly financial support for the student is equal to that of the Summer Research Fellowships. A unique feature is the possibility of continuing work in the same, or a different, lab or research office and to continue to interact with research oriented surgeons clinically throughout medical school.
Program Director: Jay Piccirillo, MD

T35 NIH NHLBI Training Grant
This program is designed to provide medical students with a hands-on research experience. This can be a first-time experience or a project related or unrelated to research done as an undergraduate. Excellent mentors from a broad range of basic and clinical sciences are available. A Washington University Summer Research Fellowship can provide a strong background for application to the MA/MD and MD/PhD (MSTP) degree programs, can lead to abstracts at meetings and to publications, and can be important for applications for competitive residencies.
Program Director: Koong-Nah Chung, PhD

T35 NIH NIDDK Short-Term Training Program
The goal of the trans-NIDDK Short-Term Training Program for Medical Students is to expose medical students to career opportunities in basic or clinical research related to diabetes, obesity, endocrine disorders, metabolic diseases, nutritional disorders, digestive diseases, liver diseases, kidney diseases, urologic diseases and hematological disorders.
Program Director: Thomas J. Baranski, MD, PhD

Abstracts for Oral Presentations

In the Order Presented

Beigelman, Avraham, MD
CRTC KL2 Career Development Awards Program
Division of Allergy, Immunology and Pulmonary Medicine
Department of Pediatrics, Washington University in St. Louis School of Medicine
Mentor: Leonard Bacharier, MD

A statistical model to improve prediction of negative oral food challenges

Beigelman A; Strunk RC; Garbutt JM; Schechtman KB; Jaenicke MW; Stein JS; Bacharier LB

Introduction: Clinical guidelines recommend that children with food-specific-IgE (FSIgE) ≤2 kUa/L to milk, egg or peanut (or ≤5 kUa/L to peanut without a history of previous reaction) are appropriate candidates for oral food challenge (OFC) to investigate tolerance to these foods. This recommendation is based on research showing that these FSIgE cutoffs are associated with approximately 50% likelihoods of negative OFC. Our goal was to develop a statistical model that improves the prediction of negative OFC compared to the current criteria using FSIgE cutoffs value alone.
Methods: We collected demographics, severity of previous reaction, history of atopic diseases, total IgE and FSIgE values, and skin tests results on children who underwent OFCs based on the recommended FSIgE cutoffs. We developed separate logistic regression models for each food for the prediction of negative OFC.
Results: 444 OFC met our inclusion criteria. The proportions of negative OFCs were 58%, 42%, and 63% to milk, egg and peanut respectively. Statistically significant predictors for negative challenges in the regression models included: lower FSIgE levels (all foods), higher total IgE (milk), consumption of baked egg products (egg), and non-Caucasian race (egg and peanut). Using these factors allowed for identification of children with the highest likelihoods of negative OFCs. These children had negative OFC 75-83% of the time.
Conclusions: OFCs conducted based upon the currently recommended FSIgE values resulted in negative OFC to milk, egg and peanut in 42-63% of the time. Our models identified combinations of prediction factors that increased the rate of negative OFC, and thus can be utilized for selection of optimal OFC candidates.

Goetzinger, Katherine R, MD
CRTC Postdoctoral Program
Division of Maternal-Fetal Medicine
Department of Obstetrics & Gynecology, Washington University in St. Louis School of Medicine
Mentors: Anthony Odibo, MD, MSCE; George Macones, MD, MSCE

Is isolated echogenic bowel an independent risk factor for intrauterine growth restriction and intrauterine fetal demise?

Goetzinger KR; Cahill AG; Macones GA; Odibo AO

Introduction: The finding of fetal echogenic bowel on second-trimester ultrasound has been associated with conditions such as cystic fibrosis, congenital infection, and aneuploidy. Prior studies have also suggested an increased risk of intrauterine growth restriction (IUGR) and intrauterine fetal demise (IUFD) in these fetuses, although precise estimates of risk for these adverse outcomes have not been quantified. The aim of this study was to determine if isolated echogenic bowel diagnosed on second-trimester ultrasound has an independent risk association with IUGR and IUFD.
Methods: This is a retrospective cohort study of all patients with a singleton gestation who presented for second-trimester ultrasound over an 18-year time period in our center. Study groups were defined by the presence of absence of echogenic bowel. Primary outcomes were IUFD at ≥20 weeks' gestation and IUGR, defined as birth weight <10^{th} percentile for gestational age on the Alexander growth curve. Univariate and multivariate logistic regression analyses were used to estimate the risk of IUFD and IUGR in fetuses with echogenic bowel. Analyses were repeated after excluding cases of aneuploidy, cytomegalovirus (CMV) infection, and other major congenital anomalies.
Results: Of 64,048 patients, the incidence of echogenic bowel was 0.4%. Of these, echogenic bowel was an isolated finding in 188 (72.3%) cases. There were 579 (0.9%) cases of IUFD and 8,173 (12.8%) cases of IUGR in the entire cohort. After excluding cases of aneuploidy and CMV infection, echogenic bowel was significantly associated with both IUFD (aOR 9.6, 95% CI 5.8-15.9) and IUGR (aOR 2.1, 95% CI 1.5-2.9) after controlling for potential confounders. This risk association remained significant even when evaluating echogenic bowel as an isolated sonographic finding.
Conclusions: The presence of isolated echogenic bowel on ultrasound is independently associated with an increased risk for both IUGR and IUFD. Serial growth assessment and antenatal testing may be warranted in cases of isolated echogenic bowel.

Liao, Steve, MD
CRTC KL2 Career Development Awards Program
Division of Newborn Medicine
Department of Pediatrics, Washington University in St. Louis School of Medicine
Mentors: Terrie Inder, MD; Joseph Culver, PhD; Jane Garbutt, MChB

Bedside resting-state functional connectivity in neonates

Liao SM; White BR; Ferradal SL; Inder TE; Culver JP

Introduction: The high incidence of adverse neurodevelopmental outcomes in preterm infants remains a major clinical problem. Defining both anatomical and functional brain lesions may help understand the neural mechanism of adverse outcomes. Recent development of functional connectivity (fc) MRI has opened a unique opportunity to study neonatal brain development at rest, however access to fixed scanners are often restricted in the sickest infants due to transport difficulties. Recent advancements in diffuse optical tomography (DOT) may provide a valuable clinical tool to evaluate neonatal brain at the bedside. Here we present the first set of fc-DOT images in term and preterm-born infants at the bedside using our novel high-density DOT device.

Methods: We recruited both healthy term-born infants and preterm infants with various brain injuries. The imaging cap was placed over the occiput recording spontaneous hemodynamic fluctuations in bilateral visual cortices at rest. We used seed-based analysis similar to fc-MRI methodology and created imaging maps of correlation r values in reference to predetermined seed regions.

Results: Healthy term infants show strong bilateral correlations between the two visual seeds in all three hemodynamic contrasts (r: 0.63-0.92). Two preterm infants with no known occipital injuries show weaker bilateral correlation values (0.55-0.85), whereas the preterm infant with left occipital stroke had only an ipsilateral correlation pattern.

Conclusions: Our study shows that functional connectivity pattern can be imaged safely at the bedside using high-density DOT. The visual network may be developmentally regulated based on our findings and can be altered by anatomical lesions and potentially other clinical factors. Future directions include expanding the imaging cap to identify resting state networks involving other regions of the brain as well as correlating functional lesions to future neurodevelopmental outcomes.

Varma, Sumeeta
Medical Student
CRTC Predoctoral Program
Department of Psychiatry, Washington University in St. Louis School of Medicine
Mentor: Linda Cottler, PhD

Willingness to participate in clinical research procedures in a community sample

Varma S; O'Leary CC; Cottler LB

Introduction: In planning clinical studies, investigators must consider the overall burden participants will bear. Ethical standards require the total risks and burdens to be outweighed by the study's benefits, and a study must have adequate enrollment to achieve its goals. In this study, we aimed to better understand how community members view research procedures and which procedures they are willing to participate in.

Methods: HealthStreet St. Louis is a Washington University initiative that uses Community Health Workers to engage St. Louisans in opportunities for research. Individuals are interviewed about health concerns, connected to services, engaged in discussion about clinical research, and asked about their willingness to participate in various types of research. Interviews follow a standardized intake form and data are entered into a central database. Chi-square tests were used to compare the proportions of respondents willing to participate in specific research activities. The Bonferroni correction for multiple comparisons was applied. Data analysis used SAS for Windows.

Results: From March 2010 to January 2011, 1429 individuals were interviewed. Mean age was 38.3±14.5 years, 56.0% were female, and 9.8% were Caucasian. Overall, 96.9% were willing to answer health questions for research, 94.4% would give a blood sample, 90.8% would undergo genetic testing, 90.1% would let researchers see their medical records, 87.9% would use medical equipment, 81.3% would stay overnight in a hospital, and 62.7% would take medicine. In pairwise comparisons, willingness was significantly lower for letting researchers see medical records than for giving a blood sample ($p<0.001$), but there was no difference in willingness between letting researchers see medical records and undergoing genetic testing ($p=0.9$). Willingness to take medicine was lower than willingness to stay overnight in a hospital ($p<0.001$).

Conclusions: Willingness to allow medical records review and to take medicine were lower than willingness to engage in other research procedures often seen as more burdensome to participants. Understanding community members' views about the acceptability of various research activities is critical to designing studies that are respectful of participants and gain their cooperation.

Willis, Allison, MD
CRTC KL2 Career Development Awards Program
Movement Disorders Division
Departments of Neurology and Neurosurgery, Washington University in St. Louis School of Medicine
Mentors: Brad A Racette, MD; Mario Schootman, PhD

Utilization of neurologists by Medicare beneficiaries for the treatment of Parkinson Disease

Willis AW; Schootman M; Evanoff B; Perlmutter J; Racette B

Introduction: Recent data indicates that the number of people with Parkinson Disease (PD) exceeds that suggested by specialty clinic surveys, suggestive of neurologist underutilization. Demonstrating that neurologist treatment improves PD outcomes would highlight the need to support the practice of neurology and neurological education. Our study objectives were to investigate the utilization of neurologist providers in the treatment of PD patients and determine if neurologist care is associated with improved clinical outcomes.

Methods: We conducted a retrospective cohort study of nearly 36 million U.S. Medicare beneficiaries aged 65 and older in the year 2002. Multilevel logistic regression was used to determine which patient characteristics predicted neurologist care between 2002 and 2005, and compare the age, race, sex-adjusted annual risk of skilled nursing facility placement, hospice placement and hip fracture between neurologist and primary care physician treated PD patients. Cox proportion hazard models determined the age, race, sex and comorbidity adjusted six year risk of death using incident PD cases, stratified by physician specialty.

Results: Over 469,000 PD cases were identified. Only 58% of PD patients received neurologist care between 2002 and 2005. Race and sex were significant predictors of neurologist treatment, with women and non whites 28 and 32 percent less likely to be treated by a neurologist during the study period. Neurologist treated patients were 36% less likely to be placed in a skilled nursing facility (OR 0.64, 95%CI: 0.62-0.66), and had 45% lower likelihood of hospice care (OR 0.56, 95%CI: 0.54-0.57). Additionally, neurologist treated patients had a 19% lower likelihood of hip fracture (OR 0.81, 95%CI: 0.77-0.87) and a 37% lower likelihood of death (OR 0.63, 95CI:0.63-0.64).

Conclusions: Women and minorities with Parkinson Disease obtain specialist care less often than white men. Neurologist care of PD patients is associated with improved selected clinical outcomes and greater survival. This may reflect optimized medical management for those who see neurologists.

Abstracts for Poster Session

Alphabetically by Training Program and Author

American Association of Neurological Surgeons (AANS)

109 **Greenberg, Jacob K**

Medical Student
Dean's Fellowship; AANS
Summer Research Program
Department of Neurological Surgery, Washington University in St. Louis School of Medicine
Mentor: Gregory J. Zipfel, MD

The role of endogenous protection against subarachnoid hemorrhage

Greenberg JK; Milner E; Vellimana AK; Han BH; Zipfel GJ

Introduction: Aneurysmal subarachnoid hemorrhage (SAH) is a devastating condition associated with high mortality and morbidity as a result of the initial aneurysmal rupture as well as from delayed cerebral ischemia that develops in the days after rupture, largely due to spasm of large cerebral arteries. Recent evidence suggests that hypoxic preconditioning (PC) is capable of augmenting the brain's endogenous protective mechanisms against ischemia. One candidate inducer of this pathway is hypoxia-inducible factor 1 (HIF-1). In this study, I develop a technique for comparing levels of gene expression in the cerebral vasculature, examine the role of HIF-1 in the context of SAH, and test the potential for ischemic post-conditioning following SAH.

Methods: Real time quantitative PCR (RT-qPCR) was used to quantify differences in gene expression in mouse brain parenchyma and vasculature. 2-methoxyestradiol was used as a selective HIF-1 inhibitor. Ischemic post-conditioning was performed by occlusion of the common carotid artery immediately following SAH surgery.

Results: The RT- qPCR technique was verified by 128 fold enrichment of a vessel-specific gene in vessel samples relative to brain parenchyma. This technique was also verified by the up-regulation (2.4 fold) of adrenomedullin and lack of significant change in HIF-1 in preconditioned mouse brains, consistent with previously published results. In addition, early results suggest that pharmacologic inhibition of HIF-1 abrogates the protection against SAH mediated by hypoxic PC (38% loss of PC-induced protection in mice treated with 2ME2 during hypoxia). Finally, preliminary results suggest that hypoxic post-conditioning can afford similar protection against SAH-induced damage as hypoxic PC (70% reduction in SAH-induced neurological deficit; 44% reduction in SAH-induced vasospasm).

Conclusions: This study demonstrates the utility of RT-qPCR as a technique for measuring differences in gene expression among samples of brain vessels and parenchyma. In addition, the partial abrogation of PC-induced protection by HIF-1 inhibition suggests HIF-1 may play an important role in endogenous protection against SAH. Finally, the protection against SAH afforded by hypoxic post-conditioning suggests the therapeutic potential of manipulating the brain's endogenous protection systems following SAH. Combined, these results lay the foundation toward identifying therapeutic targets to mitigate the harm caused by SAH.

Center for Health Policy

053 **Askin, Elisabeth**
Medical Student
Dean's Fellowship
Summer Research Program
Center for Health Policy, Washington University in St. Louis
Mentor: William Peck, MD
The Askin-Moore Guide to the US health care system
Askin ET; Moore NH; Peck W
Introduction: Health care in America is a vast and complicated system currently undergoing great change. Health professionals hold enormous power in shaping not only the structure of this system and its reform but, further, shaping public opinion. Yet these health professionals learn little about the system while in school, often entering their respective fields largely ignorant of what makes the system work and what its shortcomings are. This is a problem Mr. Moore and I set out to solve.
Methods: Without long-term experience and study, it can be difficult to cobble together an understanding of what health care even *is*. News, popular books, and scholarly works usually focus on different aspects of care, making it tricky to connect the dots and see the big picture. But we should make it as easy as possible to understand the US health care system. The goal of this book is to provide an overview of facts, concepts, and analysis, akin to a dummy's guide.
Results: The book is four chapters and 125 pages. Chapter 1 begins with health care systems and delivery; that is, explaining what the types of hospitals, clinics, and doctor's offices are, how they are structured, and what their health workstaff do. Chapter 2 addresses different types of insurance, how people access care, basic economic principles, and why health care is so expensive. Chapter 3 covers the research system: what types of research there are, how they get funded, and how they become usable treatments and guidelines. Chapter 4 breaks down the reform laws of 2010, explaining how things will change and what some criticisms are. Each chapter also addresses several relevant problems and issues (such as hospital-acquired infections, medical malpractice, research validity, and uncontrolled costs), providing point-counterpoint structure for balance.
Conclusions: The book is ordered as a progression of knowledge, but it is separated into discrete sections so readers may easily supplement what they already know without reading cover-to-cover. Further, each chapter ends with a Suggested Reading list, offering avenues for interested readers to go beyond the scope of the book. Ultimately, the book should offer readers sufficient background to develop informed opinions and evaluate structure and policy issues.

092 **Chen, Chris**
Medical Student
Dean's Fellowship
Summer Research Program
Center for Health Policy, Washington University in St. Louis
Mentors: William Peck, MD; Cindy Chen
The impact of biosimilar drugs on access, cost, and innovation in the European Union
Chen C; Chen C; Peck W
Introduction: The 2009 Biologics Price Competition and Innovation Act (BPCIA) authorized the FDA to develop a formal pathway for approving biosimilars. However, the much more complex development and manufacturing process of biologic drugs versus small molecule drugs creates unique regulatory and economic challenges to shaping an approval pathway. Because of this, the impact generics have had on the US small molecule market may not be predictive of the impact biosimilars will have on the US biologic market. We therefore study the biosimilars experience of European Union-5 (UK, France, Germany, Spain, and Italy) to help predict how FDA approval of biosimilars will affect access, costs, and innovation of biologic drugs in the US.
Methods: We conducted a systematic literature review of differences between the European Union and US biosimilar scientific, regulatory, and legal policies. We then used pharmaceutical industry data to create country- and drug class-specific scorecards to evaluate the relative success of the EU-5 biosimilar markets in achieving improved access, decreased cost, and preserved innovation.
Results: Despite sharing a single centralized drug approval agency, the EU-5 has experienced highly variable biosimilar market penetration and pricing across different member countries and different drug classes.
Conclusions: The large variability in biosimilar uptake across the EU-5 suggests that non-regulatory cultural factors such as physician and patient confidence in biosimilars may be crucial for encouraging their clinical use.

CRTC KL2 Career Development Awards Program

043 **Camins, Bernard C, MD, MSCR**
CRTC KL2 Career Development Awards Program
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Daniel Brennan, MD; Victoria Fraser, MD
Treatment and outcomes of invasive Candidiasis at a tertiary care center
Camins BC; Kuo EJ; Puzniak LA; Doherty JA; Reichley RM
Introduction: Mortality rate from invasive candidiasis has historically been high. The objective of this was to characterize the use of antifungals in the treatment of patients with invasive candidiasis (IC) or candidemia (C) using only electronic data.
Methods: We performed a retrospective cohort study of patients with IC or C who were admitted to a 1250-bed tertiary care center from 10/1/2004 to 12/31/2009. Only electronic data was used for this study. Multivariate analyses were performed using Cox Proportional Hazards modeling (independent outcome was 28-day mortality) and Logistic regression modeling (independent outcome was microbiological failure or 28-day mortality). A *P*-value of <0.05 was considered statistically significant.
Results: 963 patients met our study definition. Mean age was 57 + 16 years (17-96 years). 66% (634/963) had candidemia while 34% (328/963) had invasive candidiasis without candidemia. The 28-day mortality rate was 25% (244/963) and microbiological failure rate was 36% (343/963). Antifungal agents prescribed, defined as a single active agent for 10 consecutive days, were fluconazole (19%; 184/963), anidulafungin (9%; 86/963), caspofungin (5%; 44/963), voriconazole (<1%; 4/963), and amphotericin B (<1%; 2/963). The rest of the patients were treated with multiple agents, less than 10 consecutive days, or inappropriate agents. On both multivariate analyses, significant predictors of 28-day mortality or microbiological failure included admission to the ICU, a longer length of stay, a higher modified Apache II score, C vs. IC only, hepatic dysfunction, and malignancy. Only treatment with anidulafungin for at least 10 consecutive days after the positive culture was associated with increased survival at 28 days or microbiological cure.
Conclusions: Mortality among patients with invasive candidiasis remains high (25%). Predictors for mortality or microbiological failure included admission to the ICU, a longer length of stay, a higher modified Apache II score, candidemia vs. invasive candidiasis only, hepatic dysfunction, and presence of malignancy while treatment with anidulafungin was associated with increased survival or microbiological cure.

No Poster Displayed

Foster, Erin, OTD, MSCI
CRTC KL2 Career Development Awards Program
Program in Occupational Therapy, Washington University in St. Louis School of Medicine
Mentors: Tamara Hershey, PhD; Joel Perlmutter, MD
Instrumental activities of daily living performance in Parkinson's disease without dementia.
Foster ER; Watkins J; Hershey T; Perlmutter J
Introduction: Executive functions orchestrate instrumental activities of daily living (IADL), which are essential for productive and independent living. Non-demented individuals with Parkinson disease (PD) reliably demonstrate executive function deficits on neuropsychological tests, but the impact of these deficits on real-world functional performance is unclear. We are conducting a study to determine the relationship between executive dysfunction and IADL performance in PD.
Methods: Twelve non-demented individuals with PD (age: M=61.3, SD=4.9; 50% female) have undergone executive function and IADL assessment using standardized performance-based tests. The IADL test employs a graded cueing system if the participant cannot complete the task independently (0=completely dependent, 3=independent). A preliminary exploration of the data from one executive function test (attentional set shifting) and three IADL tests (medication management, money management, meal preparation) is reported here. Non-parametric analyses were used.
Results: Average independence scores on the tasks ranged 2.87-2.98, indicating high performance overall. Cues were required by 33-42% of participants to complete the various tasks. Participants were grouped according to whether or not they required cues to complete each task. Motor and executive function scores were then compared across these groups. Severity of motor impairment was not different across groups for any of the tasks (ps > 0.20). Executive function scores were worse for participants who needed cues to complete the meal (p = 0.01) and medication (p = 0.05) tasks.
Conclusions: Even in the absence of dementia, mild cognitive deficits may impair daily function in individuals with PD. A better understanding of the relationship between executive dysfunction and IADL performance in this population is warranted. Future results will guide development of more comprehensive occupational therapy programs to improve function and quality of life for individuals with PD.

019 **Holtz, Lori, MD**

CRTC KL2 Career Development Awards Program
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Mentors: David Wang, PhD; Phillip Tarr, MD

Epidemiology of newly discovered astrovirus, MLB1

Holtz L; Bauer I; Rajendran P; Belshe R; Schultz-Cherry S; Kang G; Wang D; Tarr P

Introduction: Diarrhea is the third leading infectious cause of death worldwide. Astroviruses, noroviruses, adenoviruses, and rotaviruses are the major diarrheagenic viruses. However, ~40% of diarrhea is of unknown etiology. We have recently discovered five highly divergent astroviruses, MLB1, MLB2, VA1, VA2, and VA3 in stools of children with diarrhea. The purpose of this study is to define the frequency at which MLB1 infects humans and to determine if MLB1 is associated with human diarrhea.

Methods: To define the frequency at which MLB1 infects humans, I have developed an indirect ELISA to determine the seroprevalence of MLB1. I have used this assay to study age stratified serum samples from subjects enrolled in vaccine trials. To assess if MLB1 is associated with diarrhea, viral prevalence in a case-control cohort was determined. Stool samples were evaluated from a longitudinal birth cohort study in Vellore, India. 400 diarrhea (case) stools and 400 paired non-diarrheal (control) stools obtained from the same child at least six weeks prior were examined by RT-PCR for these five new astroviruses.

Results: MLB1 infection appears to occur commonly in the general population. Specifically, MLB1 seropositivity in this cohort was 100% by adulthood. Additionally, seropositivity was high in the youngest age group (<6 months) suggesting that maternal antibodies are transmitted. No cross reactivity was seen with human astrovirus 1 or MLB2. RT-PCR of the case control stools showed that 14/400 cases were positive for the classic human astroviruses while 4/400 controls were positive (p=0.029). However, 4/400 cases and 14/400 controls were positive for MLB1 (p=0.033).

Conclusions: The data gathered from these efforts are the first to describe if these viruses are potentially human pathogens and if they are associated with diarrhea. While results from this study suggest that MLB1 is not associated with diarrhea, data from this seroprevalence study suggests that exposure to MLB1 is ubiquitous. The role of MLB1 in human health is still not established.

004 **Lindman, Brian R, MD**

CRTC KL2 Career Development Awards Program
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Douglas Mann, MD; Brian Gage, MD

Low stroke volume index is associated with a low transvalvular gradient and predicts survival in patients with severe aortic stenosis

Lindman BR; Madrazo JA; Novak E; Johnson SN; Holland MR; Miller JG; Zajarias A; Hohn TA; Pérez JE; Arnold SV

Introduction: In patients with severe aortic stenosis (AS), a low transvalvular mean gradient (MG) is associated with worse outcomes, but the factors that influence the MG remain incompletely understood. Both low flow and increased afterload have been associated with a low MG. We explored the relative importance of flow (as measured by stroke volume index [SVI]) and afterload on MG and survival in patients with severe AS.

Methods: Clinical and echocardiographic data were prospectively obtained on 168 patients with severe AS (indexed AVA [AVAi] <0.6 cm^2/m^2). Multivariable linear regression models investigated predictors of MG and SVI. A Cox proportional hazards model explored the association of SVI with all-cause mortality; mean follow-up = 1 year.

Results: A low MG (<40 mmHg) was observed in 77% of patients with ejection fraction (EF) <50% (n=66) and in 40% with EF ≥50% (n=102). After controlling for AVAi and ejection time, a lower SVI was associated with a reduced MG (ß=-1.92 mmHg, p<0.001), whereas arterial afterload variables [systemic vascular resistance (SVR), systemic arterial compliance (SAC), mean arterial pressure (MAP), history of hypertension] were not associated with MG (R^2=0.80). However, in a separate model predicting SVI, after controlling for AVAi and variables reflecting LV preload, remodeling, and function, the arterial afterload variables SVR, SAC, and MAP were associated with SVI (p<0.001 for all; R^2=0.83). Patients with SVI <30.7 ml/m^2 had reduced 1-year survival compared with SVI ≥30.7 (65% vs. 85%, p=0.005). After adjusting for age, reduced EF, prior infarct, aortic valve replacement, valvuloarterial impedance and SAC index, every 5 ml/m^2 reduction in SVI was associated with a 45% increase in the hazard of death (95% CI 1.01-2.08, p=0.046). Increased arterial afterload was not associated with an adverse prognosis in this model.

Conclusions: A low MG is common in patients with a small AVA, regardless of EF and is directly related to a reduced SVI, but not arterial afterload. A reduced SVI reflects failing compensatory mechanisms and is associated with worse survival. This simple echocardiographic measurement may improve clinical management in patients with severe AS.

128 **Maccotta, Luigi, MD, PhD**

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Mentors: Ed Hogan, MD; Maurizio Corbetta, MD

Regional network disruption in temporal lobe epilepsy

Maccotta L; Corbetta M; Hogan RE

Introduction: Medial temporal cortex forms a network of anatomical connections with both the contralateral medial temporal lobe and with other temporal brain regions. Regions outside the temporal lobe, such as the insula, have shown a clear role in the ictal period (Hogan et al. 2006), with both semiologic and electrographic correlates in epileptic seizures. It is unclear whether the medial temporal cortex and other temporal and extratemporal brain regions form a functional network, and how temporal lobe epilepsy (TLE) affects these connections. Here we investigated the functional connections of the medial temporal region with contralateral temporal and extratemporal brain regions in TLE patients and healthy controls using resting state blood-oxygenation-level-dependent (BOLD) functional MRI.

Methods: Thirty-two TLE patients underwent resting-state BOLD fMRI. Seizure localization was based on video-EEG. Healthy controls served as comparison. Regions of interest were defined anatomically a priori and functioned as seeds in a functional connectivity analysis.

Results: TLE is associated with changes in the network connections of the medial temporal region. Healthy hippocampal and parahippocampal regions exhibit strong symmetric coupling across hemispheres. With TLE this strong symmetric connectivity is significantly decreased ($p<.05$), resulting in a functional decoupling between medial temporal regions. More locally, decoupling is also observed within each medial temporal region. Conversely, the medial temporal region ipsilateral to the epileptogenic focus exhibits significantly increased coupling with the bilateral insulae (and to a lesser extent with the entorhinal cortex).

Conclusions: This surprisingly increased functional connection in the face of a pathologic and often destructive process has several possible explanations, including a maladaptive-pathologic etiology, possibly representing abnormal circuitry that is involved in seizure generation. Alternatively it may represent a compensatory response, such as an attempt at down-modulation of a pathologically excitable circuit. These additional nodes in the functional network of TLE may provide future pharmacologic and surgical targets.

044 **Marschall, Jonas, MD**

CRTC KL2 Career Development Awards Program
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Mentor: David Warren, MD, MPH

A retrospective comparison of ceftriaxone versus oxacillin for osteoarticular infections due to methicillin-susceptible *Staphylococcus aureus*

Wieland B; Marcantoni JR; Bommarito KM; Warren DK; Marschall J

Introduction: Antistaphylococcal penicillins are the treatment of choice for infections due to methicillin-susceptible *Staphylococcus aureus* (MSSA). Another β-lactam, ceftriaxone, can be dosed once a day and is less expensive for outpatient intravenous (IV) therapy than oxacillin. Our objective was to evaluate patient outcomes using ceftriaxone vs. oxacillin for treatment of MSSA osteoarticular infections (OAI).

Methods: We retrospectively reviewed medical records of patients (pts) diagnosed with MSSA OAI at a tertiary care hospital from 1/2005-4/2010. We collected demographic, clinical, and outcome data including treatment-related adverse events. Successful treatment (clinical improvement; improved follow-up markers & imaging; no readmission for treatment) was compared at early follow-up (3-6 months) and late follow-up (6+ months) after completion of IV antibiotics.

Results: 124 pts had an MSSA OAI. Median age was 53 years (range 18-85). 90 pts were diagnosed with osteomyelitis (73%) & 57 with septic arthritis (46%). 64 (52%) had orthopedic hardware involvement. 74 (60%) pts were treated with ceftriaxone & 50 (40%) with oxacillin. Median duration of IV antibiotics was 43 days (range, 22-132). Oxacillin was more often discontinued due to toxicity [11/50 (22%) oxacillin vs. 4/74 (5%) ceftriaxone; p=0.005]. At early and late follow-up, data for 97 and 88 pts were available for analysis, respectively. Treatment success was similar between groups at early follow-up [50/60 (83%) ceftriaxone vs. 32/37 (86%) oxacillin; p=0.7] and late follow-up [43/56 (77%) ceftriaxone vs. 26/32 (81%) oxacillin; p=0.6].

Conclusions: To our knowledge, this is the first comparison of ceftriaxone to oxacillin for MSSA osteoarticular infections with regard to patient outcomes. There was no difference in outcomes between the treatment groups at early and late follow-up visits after the completion of IV antibiotics. Pts receiving oxacillin were more likely to have it stopped due to toxicity. Additional trials are warranted to establish ceftriaxone as an equivalent treatment option.

077 **Pepino, M Yanina, PhD**

CRTC KL2 Career Development Awards Program
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Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Nada Abumrad, PhD; Todd Braver, PhD

A variant in the lipid-binding protein CD36 and a lipase inhibitor affect oral sensitivity to fat in obese subjects

Pepino MY; Love-Gregory L; Klein S; Abumrad N; Braver T

Introduction: CD36 and salivary lipase are critical for orosensory detection of fat, which is mediated by fatty acids (FA) as the signaling stimulus, and they modulate fat preference in rodents. However, their potential role in humans' fat orosensory perception remains completely unknown. We hypothesized that a common SNP (rs1761667) in the CD36 gene that reduces CD36 expression or the addition of orlistat, a lipase inhibitor, to reduce hydrolysis and FA release from triacylglycerols (TAG), the main component of dietary fats, would attenuate fat taste sensitivity.

Methods: Twenty one obese subjects with rs1761667 genotypes (6 AA, 7 AG and 8 GG) were studied on two occasions in which oleic acid and triolein orosensory detection thresholds were measured using emulsions prepared with and without orlistat.

Results: Subjects homozygous for the G-allele had lower detection thresholds for oleic acid and triolein than subjects homozygous for the A allele, which associates with lower CD36 expression. The thresholds for heterozygous subjects were intermediate (log threshold AA= 0.1±0.2, AG= -0.5±0.2 and GG= -0.8±0.2; p=0.03). Addition of orlistat to fat emulsions increased detection thresholds (i.e. diminished orosensory sensitivity) to triolein (log threshold with orlistat= -0.3±0.2 without= 0.3±0.1 $p<0.001$) but not oleic acid (log threshold with orlistat= -1.0±0.2 without= -0.8±0.2 $p>0.2$).

Conclusions: This is the first experimental evidence for a role of CD36 and lingual lipase in fat gustatory perception in humans. A better understanding of the mechanisms involved in fat sensory perception may be critical for targeting early control steps in fat intake and absorption which could lead to better treatments for obesity and other metabolic diseases.

133 **Pruitt, Sandi L, PhD, MPH**

CRTC KL2 Career Development Awards Program
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Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Nicholas Davidson, MD; Mario Schootman, PhD

The effect of delays in the diagnosis and treatment of colorectal cancer on cancer-specific and all-cause risk of death

Pruitt SL; Harzke AJ; Davidson NO; Schootman M

Introduction: The effect of delays in the diagnosis and treatment of colorectal cancer (CRC) on risk of death is unclear. We examined the effect of such delays on risk of death in a U.S. population-based sample of older adults with colon or rectal cancer.

Methods: Using the 1998-2005 linked SEER-Medicare data, we examined the effect of diagnosis and treatment delays on cause-specific and all-cause risk of death among U.S. adults aged ≥66 years with a first primary colon or rectal cancer. We assessed diagnosis and treatment delays as time in days between (1) initial medical consult for CRC symptoms and pathologically confirmed diagnosis (maximum: 365 days) and (2) pathologically confirmed diagnosis and death and/or censored outcome (maximum: 120 days). We examine the effect of both long and short delays on the risk of death separately for colon and rectal cancer. Cases (deaths from each specific cause) and controls (patients who died of other causes or were censored) were matched on survival time. Logistic regression models adjusted for sociodemographic, tumor-related, treatment-related, and neighborhood-level factors.

Results: F or the 11,169 identified and eligible patients, median delays were as follows: diagnostic delays were 59 (colon) and 40 (rectal) days and treatment delays were 14 (colon) and 18 (rectal) days. For colon cancer patients, neither diagnostic nor treatment delays were associated with cause-specific death after adjustment for confounders in final models. However, compared to those with diagnosis delays of 14-30 days, those colon cancer patients with shortest (<2 weeks) and longest (≥8 months) diagnosis delays experienced a higher risk of all-cause (but not cause-specific) death in the final models ([OR: 1.30; CI: 1.04-1.62], [OR: 1.38; CI: 1.12-1.71] respectively). Diagnosis and treatment delays were not associated with increased risk of either all-cause or cause-specific death for rectal cancer patients.

Conclusions: Delays of up to 1 year for diagnosis and up to 120 days for treatment did not appear to affect risk of death for CRC patients.

046 **Riddle, David, MD**

CRTC KL2 Career Development Awards Program
Division of Infectious Diseases
Department of Internal Medicine, Washington University School of Medicine
Mentors: Michael Caparon, PhD; David Hunstad, MD

Variation in Streptococcus pyogenes virulence genes is associated with invasive infections and tissue tropism

Riddle DJ; Bessen DE; Caparon MG

Introduction: *Streptococcus pyogenes* causes a wide variety of diseases, commonly infecting the throat or skin. The factors that determine tissue tropism and disease severity are poorly understood. *S. pyogenes* NAD^+ glycohydrolase (*spn*), Streptolysin O (*slo*), Streptolysin S (*sls*, sag operon), Streptococcal pyrogenic exotoxin B (*speB*), Streptokinase (*ska*), Streptodornase (*sda1*), and the CovR/S transcriptional regulators are virulence related genes implicated in the pathogenesis of invasive streptococcal infections. We hypothesize that polymorphisms in these genes contribute to invasive streptococcal diseases or to the organism's tissue tropism. Our study will identify the genetic differences between strains that cause invasive and noninvasive infections and reveal patient characteristics that increase the risk of invasive streptococcal disease.

Methods: We will sequence *spn*, *ifs*, *slo*, *sls*, *speB*, *ska*, *sda1*, and *CovR/S* from worldwide and local collections of *S. pyogenes*. Invasive and noninvasive strains will be matched by *emm* pattern, *emm* type, and housekeeping gene similarities to reduce the background genetic variation. Polymorphisms associated with invasive diseases or tissue tropism will be uncovered. Patient characteristics associated with invasive diseases will be identified using statistical analyses.

Results: Initial analysis of *spn* revealed that this virulence factor is evolving under positive selection, diverging into NAD^+ glycohydrolase (NADase)-active and -inactive subtypes. NADase activity did not correlate with invasive disease in our worldwide collection but was associated with tissue tropism. We anticipate uncovering novel functionally significant polymorphisms in the other virulence genes being studied. We also anticipate identifying patient characteristics that are associated with susceptibility to invasive streptococcal infection.

Conclusions: These findings will identify virulence factors involved in invasive streptococcal diseases so that novel therapeutics that target these proteins may be developed. We also anticipate identifying risk factors that may be controlled during periods of increased streptococcal infections.

078 **Riek, Amy E, MD**

CRTC KL2 Career Development Awards Program
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Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Carlos Bernal-Mizrachi, MD

Vitamin D sufficiency is associated with an anti-atherogenic monocyte/macrophage phenotype in type 2 diabetic patients

Riek AE; Oh J; Timpson A; Bernal-Mizrachi C

Introduction: Cardiovascular disease (CVD) is the leading cause of morbidity/mortality in patients with type 2 diabetes mellitus (T2DM), but the mechanisms of the increased susceptibility to vascular inflammation and atherosclerosis in these patients are unclear. In T2DM, the prevalence of 25-hydroxy vitamin D [25(OH)D] deficiency is almost twice that for non-diabetics, and low vitamin D levels nearly double the relative risk of developing CVD compared to diabetic patients with normal vitamin D levels. We tested the hypothesis that monocytes from vitamin D-deficient subjects will have a pro-atherogenic phenotype compared to those from vitamin D-sufficient subjects.

Methods: We performed a cross-sectional study in 43 patients from the outpatient clinic with a self-reported diagnosis of type 2 diabetes. Monocytes were isolated from a single venous blood draw and subjected to assays for adhesion, migration, membrane receptor expression, and mRNA expression.

Results: Serum 25(OH)D level independently and inversely predicted monocyte adhesion (to fibronectin or human endothelial cells) and migration even after adjustment for age, race, and CV risk factors ($p<0.05$ for all outcomes). 25(OH)D level was also an independent predictor of the ratio of macrophage M1/M2 markers (expression of CCR7 plus CD86 over CD163 plus mannose receptor) in monocytes after adjustment for age, race, and CV risk factors ($p<0.002$), and the M1/M2 ratio correlated inversely with monocyte adhesion and migration ($p<0.03$ for all). Vitamin D-sufficient patients [25(OH)D level >30 ng/mL] had lower monocyte endoplasmic reticulum (ER) stress and decreased mRNA expression of monocyte adhesion molecules α_1-integrin, α_2-integrin, and PSGL-1 and monocyte migration receptor CCR2 compared to patients with vitamin D levels <20 ng/mL ($p<0.001$ for all). Moreover, in culture-derived macrophages, $1,25(OH)_2D_3$ suppressed ER stress, increased the M1/M2 phenotype ratio, and reduced adhesion and migration when compared to macrophages cultured without $1,25(OH)_2D_3$.

Conclusions: Vitamin D is a natural ER stress reliever that induces an anti-atherogenic monocyte/macrophage phenotype in patients with type 2 diabetes, and further study through interventional trials is needed.

057 **Stamatakis, Katherine A, PhD, MPH**
CRTC KL2 Career Development Awards Program
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Mentors: Ross C Brownson, PhD; Graham A Colditz, MD, DrPH

Measurement properties of a novel survey to assess stages of organizational readiness for evidence-based practice in community-level prevention programs

Stamatakis KA; McQueen A; Filler C; Boland B; Dreisinger M; Luke DA; Brownson RC

Introduction: There is a great deal of variation in the existing capacity of primary prevention programs and policies addressing chronic disease to deliver evidence-based practice (EBP). In order to develop and evaluate implementation strategies that are tailored to the appropriate level of capacity, there is a need for an easy-to-administer tool to stage organization readiness for delivering EBP.

Methods: Based on theoretical frameworks including Roger's Diffusion of Innovations, we developed a survey instrument to measure four domains representing stages of readiness for evidence-based practice: awareness, adoption, implementation, and maintenance. A fifth domain representing organizational climate and other program characteristics that were hypothesized to serve as mediators or moderators of readiness for EBP were also included in the survey. Twenty-six questions comprised the five domains of three to nine items each using a seven-point response scale. Representatives from obesity, asthma, diabetes, and tobacco prevention programs serving diverse populations in the United States were surveyed (N=243); test-retest reliability was assessed with 92 respondents.

Results: Confirmatory factor analysis (CFA) and structural equation models (SEM) were used to test and refine readiness scales. Test-retest reliability of the readiness scales as measured by intraclass correlation ranged from .47-.71. CFA found good fit for the five-item adoption and implementation scales, and resulted in revisions of the awareness and maintenance scales. The awareness scale was split into two two-item scales, representing community and agency awareness. The maintenance scale was split into five- and four-item scales, representing infrastructural maintenance and evaluation maintenance, respectively. Internal reliability of scales (Chronbach's α) ranged from .66-.78. The SEM for the final revised scales approached good fit, with most factor loadings >.6 and all >.4.

Conclusions: The lack of adequate measurement tools hinders progress in dissemination and implementation research. These results help fill this gap by describing the reliability and measurement properties of a theory-based tool; the short, user-friendly instrument may be useful to researchers and practitioners seeking to assess organizational readiness for evidenced-based practice across a variety of chronic disease prevention programs and settings.

No Poster Displayed

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CRTC KL2 Career Development Awards Program
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Mentor: Mario Schootman, PhD

Population-based comparative effectiveness of transurethral resection of the prostate and laser therapies for benign prostatic hyperplasia

Strope SA; Yang L; Nepple KG; Andriole GL; Owens PL

Introduction: As the American population ages, benign prostatic hyperplasia (BPH) and its associated lower urinary tract symptoms (LUTS) have become increasingly important causes of chronic morbidity. We assessed the comparative effectiveness of two common forms of surgical therapy, transurethral resection of the prostate (TURP) and laser therapies for BPH.

Methods: Using patient level discharge data and revisit files from the Agency for Healthcare Research and Quality, we evaluated a cohort of patients who underwent TURP or laser therapy for BPH in 2005 in California. Short-term outcomes (in-hospital complications, length of stay, 30-day readmission, 30-day repeat surgery, 30-day emergency room visits) were compared between the therapies through regression analysis. Long-term retreatment (defined as absence of secondary procedures for BPH or complications of therapy) was assessed with survival analysis. Analyses were adjusted for medical comorbidity, race, age, and insurance status.

Results: From 11,645 discharges, mean length of stay was shorter for laser patients versus TURP [0.70 versus 2.03 days respectively, ($p < 0.0001$)]. 30-day revisits occurred in 16% of laser patients and 17.7% of TURP patients ($p = 0.0338$). Retreatment rates at 4 years were 8.3% for TURP and 12.8% for laser ($p < 0.0001$). After adjustment, TURP patients were 37% less likely to require repeat therapy than laser patients (HR 0.64; $p < 0.0001$).

Conclusions: Laser procedures and TURP both provide effective management of BPH/LUTS. Laser procedures are associated with less need for hospitalization then TURP, but appear to involve a tradeoff in long term efficacy.

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Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Samuel Klein, MD; John Holloszy, MD

Randomized trial of exercise on intrahepatic triglyceride and lipid kinetics in nonalcoholic fatty liver disease

Sullivan S; Kirk P; Mittendorfer B; Patterson BW; Klein S

Introduction: Nonalcoholic fatty liver disease (NAFLD) and alterations in hepatic lipoprotein kinetics are common metabolic complications associated with obesity. Lifestyle modification involving diet-induced weight loss and regular exercise decreases intrahepatic triglyceride (IHTG) content and VLDL-triglyceride (TG) secretion rate. The aim of this study was to evaluate the weight loss-independent effect of following the physical activity guidelines recommended by the Department of Health and Human Services on IHTG content and VLDL kinetics in obese persons with NAFLD.

Methods: Eighteen obese people (BMI=38.1±4.6 kg/m^2) with NAFLD were randomized to 16 weeks of exercise training (45-55% $\dot{V}O_{2peak}$, 30-60 min x 5 days/week; n=12) or observation (control; n=6). Liquid formula dietary supplements were provided to prevent exercise-induced weight loss. Magnetic resonance spectroscopy and stable isotope tracer infusions in conjunction with compartmental modeling were used to evaluate IHTG content and hepatic VLDL-TG and apolipoprotein B-100 (apoB-100) secretion rates.

Results: Exercise training resulted in a 10.3±4.6% decrease in IHTG content ($p<0.05$), but did not change total body weight (103.1±4.2 kg and 102.9±4.2 kg before and after training) or % body fat (38.9±2.1% and 39.2±2.1% before and after training). Exercise training did not change VLDL-TG secretion rate (17.7±3.9 µmol/min and 16.8±5.4 µmol/min before and after training) or VLDL-apoB-100 secretion rate (1.5±0.5 nmol/min and 1.6±0.6 nmol/min before and after training).

Conclusions: Following the DHHS recommended physical activity guidelines has small but beneficial effects on IHTG content, but does not improve hepatic lipoprotein kinetics, in obese persons with NAFLD.

CRTC Postdoctoral Program

029 **Ahmad, Fahd, MD**
CRTC Postdoctoral Program
Division of Pediatric Emergency Medicine
Department of Pediatrics, Washington University in St. Louis School of Medicine
Mentors: David Jaffe, MD; Jane Garbutt, MD
Computer-assisted self-interviews improve testing for chlamydia and gonorrhea in the pediatric emergency department
Ahmad FA; Jaffe DM
Introduction: *Chlamydia trachomatis* and *Neisseria gonorrhea* are sexually transmitted infections (STIs) with a high-burden of disease, with over one-million cases in people 15-24 reported to the CDC in 2009. Untreated women may have abdominal pain, pelvic inflammatory disease, or infertility. Despite liberal screening recommendations, many adolescents are not tested. The emergency department (ED) offers a venue to test patients for STIs, regardless of reason for visit. We hypothesize that an Audio computer-assisted self-interview (ACASI) can obtain STI risk information, and increase STI testing for adolescents with indications for testing. The objective is to evaluate whether an ACASI can be implemented in a pediatric ED, and to measure the effect of an ACASI on STI testing rates in adolescents.
Methods: We created an ACASI that took a sexual history, and created an integrated software decision algorithm to provide a recommendation as to whether STI testing was indicated. Beginning in April 2011, we enrolled a convenience sample of male and female ED patients ages 15-21, regardless of chief complaint. A summary of the recommendation and patient answers was integrated into the electronic medical record, where physicians and nurse practitioners were able to review the information and test those in need. The primary outcome is rate of testing in all ACASI eligible patients compared to historical controls in the 15 months prior to the ACASI.
Results: We enrolled 471 patients though August 2011, and analyzed 460 (9 multiple enrollments and two ineligible patients were excluded). 237/460 (51%) had testing recommended, 133/237 (56%) received testing when indicated, and 26/133 (20%) had an STI. 385/460 (84%) patients had chief complaints with low likelihood of STI, of which 189/385 (49%) had testing recommended, 92/189 (49%) received testing when indicated, and 18/92 (20%) had an STI. The overall ED testing rate was 9% in controls and 16% after intervention. 35% of enrolled patients were tested, and 10% of eligible patients not enrolled were tested.
Conclusions: An ACASI was successfully implemented and significantly increased STI testing.

No Poster Displayed

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Department of Neurology, Washington University in St. Louis School of Medicine
Mentors: Anne Cross, MD; David Warren MD, MPH
CSF and serum levels of CXCL13 in MS and NMO
Alvarez E; Piccio L; Mikesell RJ; Klawiter EC; Parks BJ; Naismith RT; Cross AH
Introduction: CXCL13, a chemokine critical to the formation of germinal centers in lymphoid tissues, is chemotactic for B cells and implicated in the pathogenesis of multiple sclerosis (MS). Levels in cerebrospinal fluid (CSF) of MS patients are reported to be higher than in noninflammatory controls (NIC) and may be prognostic. We postulate that patients with neuromyelitis optica (NMO) have altered CXCL13 levels, as B lymphocytes appear to be involved in the pathogenesis of NMO given the presence of aquaporin-4 autoantibodies and possible effectiveness of rituximab in the treatment of NMO, which depletes B-cells.
Methods: With IRB approval, patients were consented to obtain CSF and serum. Patients with NMO (n=9), MS (n=12), NIC (n=9), and other neurological inflammatory controls (n=8) were stored at -80C. Levels of CXCL13 in serum and CSF and myelin basic protein (MBP) in CSF were determined using ELISA (R&D and Beckman Coulter, respectively. Nonparametric analyses were performed using SPSS.
Results: CSF CXCL13 levels were elevated in MS (mean 20.7 pg/ml) and NMO (160.0pg/ml) versus NIC (10.0 pg/ml), p=0.016 and p=0.012 respectively. Two NMO patients had levels >500 pg/ml, similar to that seen in one of two patients with CNS lymphoma and in a patient with viral meningitis. Serum CXCL13 levels were elevated in NMO (177.3 pg/ml) versus NIC (90.1 ng/ml), p= 0.031, but not between MS (100.8 pg/ml) and NIC, p=0.43. MBP in CSF was higher in patients with NMO (25.3 ng/ml) than in MS patients (5.7 pg/ml), p=0.028. CSF CXCL13 levels did not correlate with MBP levels.
Conclusions: Our data support reports of higher levels of CSF CXCL13 in MS compared to NIC. We also demonstrate for the first time, to our knowledge, elevated levels of CSF CXCL13 in NMO. CSF CXCL13 levels in NMO were highly variable, and were sometimes as high as in patients with CNS lymphoma or viral meningitis. CSF MBP levels were higher in NMO than MS, perhaps due to its more destructive pathology. In comparison to MS, patients with NMO had elevated CXCL13 levels in serum, likely reflecting the more systemic nature of NMO as compared to MS.

063 **Calfee, Ryan P, MD**
CRTC Postdoctoral Program
Division of Hand Surgery
Department of Orthopaedic Surgery, Washington University in St. Louis School of Medicine
Mentor: Bradley Evanoff, MD, MPH

The influence of insurance status on outpatient evaluations at a tertiary hand center

Calfee RP; Shah C; Canham CD; Wong A; Gelberman RH; Goldfarb CA

Introduction: The purpose of this study was to systematically examine the impact of insurance status on access to elective specialty surgical care among new patients presenting to a tertiary hand surgery center. We hypothesized that patients with Medicaid or without insurance would have greater difficulty accessing surgical care than privately insured patients and thus travel greater distances and present with less complex clinical conditions.

Methods: This retrospective cohort study captured all new orthopaedic hand patients (n=3988) at a tertiary center over 12 months. Patients' insurance status was categorized and clinical complexity was measured on an ordinal scale based on diagnosis and qualifying statements from the medical record. Statistical analysis quantified the effect of insurance status on distance traveled to appointments (ANOVA) and clinical complexity (chi square). Subgroup analysis examined insurance status among those traveling 150-250 miles, and differences between adult and pediatric patients.

Results: Increasing clinical complexity correlated with increasing driving distance to the appointment ($p<0.001$). The distribution of clinical complexity ratings for Medicaid and uninsured patients was similar to that of other new patients. As travel distance to appointment increased, patients with Medicaid insurance comprised a progressively greater percentage of patients seen ($p<0.001$). However, the increased percentages of Medicaid coverage (30.7%) among patients traveling 151-250 miles was similar to the expected rate (27.8%) based upon county level Medicaid participation ($p=0.85$). Findings were confirmed when stratifying patients by age (pediatric and adult).

Conclusions: Outpatient health care resource utilization is appropriate at our tertiary hand care center. Patients traveling the greatest distances to appointments demonstrate the highest levels of clinical complexity, without a disproportionate representation of Medicaid coverage.

No Poster Displayed

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Department of Anesthesiology, Washington University in St. Louis School of Medicine
Mentors: Richard S Hotchkiss, MD; Marin Kollef, MD

Outcomes associated with vancomycin levels in patients initially dosed with vancomycin in the emergency department

Fuller B; Skrupky L; McCammon C; Hotchkiss RS; Kollef M

Introduction: We have previously shown the Emergency Department (ED) dosing of vancomycin is predictive of subsequent inpatient dosing and vancomycin levels. We sought to determine the influence of vancomycin levels on outcomes, and hypothesized that sub therapeutic levels were associated with worse outcomes.

Methods: Retrospective observational cohort study of 1,915 patients that presented to the ED, were dosed with vancomycin, and had vancomycin levels checked within 5 days of admission. Patients administered vancomycin were identified via query of the ED automated dispensing system, and electronic medical records were used to establish patient demographics and treatment variables. Analysis with a generalized logit model fit by maximum likelihood was used to create a multivariable model from clinically and statistically significant predictors identified in univariate analysis. P values < 0.05 were deemed statistically significant and odds ratios with 95% confidence intervals were reported for significant contrasts. A therapeutic level was defined as 15-20mcg/ml.

Results: 322/1915 patients (16.81%) had therapeutic vancomycin levels. Compared with therapeutic levels, patients with supra therapeutic levels were more likely to spend 3 or more days in the hospital (OR 1.87, 95% CI 1.07 - 3.27, p= 0.03), have higher peak creatinine (mean 3.47) levels (OR 1.34, 95% CI 1.15 – 1.56), and die (OR 2.06, 95% CI 1.28 – 3.32, p=0.003).

Conclusions: Over dosing, and subsequent supra therapeutic levels, were associated with worse outcomes. These results are limited by the retrospective nature of the study and may reflect sicker patients in whom treating physicians opted for higher dosing to achieve more rapid attainment of target concentrations. There is little literature-based guidance with respect to empiric vancomycin dosing, as guidelines are written for patients with known *Staphylococcus aureus* infections. The result of this trial should serve as hypothesis generating for optimal empiric vancomycin dosing in patients with unknown, but clinically-suspected *S. aureus* infections.

No Poster Displayed

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Mentors: Jay McDonald, MD; Margaret Olsen, PhD, MPH; David Warren, MD, MPH

Orthopedic infections among veterans of operation enduring freedom and operation Iraqi Freedom
Liang SY; McDonald JR

Introduction: Blast injury and orthopedic trauma account for a significant portion of combat-related injuries sustained by U.S. forces serving in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF). Contamination of open wounds and extremity fractures are unfortunately common and may progress to osteomyelitis. Defining the epidemiology, healthcare utilization, and predictors of cure related to traumatic orthopedic infections is paramount to improving the morbidity and mortality of combat-wounded veterans transitioning to long-term care within the Veterans Affairs health system.
Methods: This project utilizes clinical and national administrative data obtained from multiple sources within the VA and remains a work in progress. Using ICD-9-CM diagnosis codes, we have identified a preliminary cohort of more than 1800 potential orthopedic infections. Linkage between databases will allow us to determine the prevalence, natural history, and number of hospitalizations and clinic visits incurred by veterans with traumatic orthopedic infections. Using regression analyses, we will then identify independent predictors of cure.
Results: Abstraction and validation of the first 50 cases using the electronic medical record has yielded one confirmed case of combat-related osteomyelitis and seven cases of non-combat-related osteomyelitis.
Conclusions: Further refinement of ICD-9-CM definitions and search strategy is needed to accurately and efficiently identify cases for inclusion. Once this has been achieved, we hope to provide a more comprehensive understanding of the epidemiology and healthcare burden of combat-related orthopedic infections within the VA system.

074 **Licis, Amy, MD**
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Mentors: Kelvin Yamada, MD; Stephen Duntley MD; Jane Garbutt, MBChB, FRCP, MHSc

Measuring the impact of AHI and obesity on circadian activity patterns using functional linear modeling of actigraphy data
Licis A; Wang J; Xian H; Deych E; Ding J; McLeland J; Toedebusch C; Li T; Duntley S; Shannon W; Yamada K; Duntley S; Garbutt J

Introduction: Actigraphy provides a way to objectively measure activity in human subjects. This paper describes a novel family of statistical methods that can be used to analyze this data in a more comprehensive way.
Methods: A statistical method for testing differences in activity patterns measured by actigraphy across subgroups using functional data analysis is described. For illustration this method is used to statistically assess the impact of apnea-hypopnea index (AHI) and body mass index (BMI) on circadian activity patterns measured using actigraphy in 395 participants from 18 to 80 years old, referred to the Washington University Sleep Medicine Center for general sleep medicine care. Mathematical descriptions of the methods and results from their application to real data are presented.
Results: Activity patterns were recorded by an Actical device (Philips Respironics Inc.) every minute for at least seven days. Functional linear modeling was used to detect the association between circadian activity patterns and AHI and BMI. Results indicate that participants in high AHI group have statistically lower activity during the day, and that BMI in our study population does not significantly impact circadian patterns.
Conclusions: Compared with analysis using summary measures (e.g., average activity over 24 hours, total sleep time), Functional Data Analysis (FDA) is a novel statistical framework that more efficiently analyzes information from actigraphy data. FDA has the potential to reposition the focus of actigraphy data from general sleep assessment to rigorous analyses of circadian activity rhythms.

073 **Ortinau, Cynthia, MD**

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Mentors: Terrie Inder, MD; Pirooz Eghtesady, MD, PhD

Alterations in cortical surface area and folding in infants with hypoplastic left heart syndrome

Ortinau C; Beca J; Alexopoulos D; Eghtesady P; Inder T

Introduction: Neurodevelopmental impairment is common in infants with hypoplastic left heart syndrome (HLHS). Brain Magnetic Resonance Imaging (MRI) has been used to investigate cerebral abnormalities and has demonstrated delayed brain maturation that begins in the *in-utero* environment. This study examined cortical cartography measures, a technique to evaluate cortical surface area and cortical folding, to further characterize alterations in pre-operative brain abnormalities in infants with HLHS. We hypothesized that infants with HLHS would have decreased cortical surface area and less cortical folding than control infants.

Methods: Seven infants with HLHS had pre-operative MRI performed, and eight healthy term infants underwent MRI for control purposes. Standard T2-weighted coronal and axial images were registered, summed, and resampled to 1-mm isotropic voxels and an automated segmentation was generated to outline the cortical gray matter. Manual editing was performed across all slices using Caret software to ensure accurate data. The cortical surface area and gyrification index (a ratio representing degree of cortical folding) were computed.

Results: No differences existed in gender, gestational age, or birth weight between the two groups of infants. Infants with HLHS had a larger head circumference than controls ($p<0.01$), therefore analysis was undertaken with head circumference as a covariate. Infants with HLHS trended towards a smaller cortical surface area ($p=0.07$), and smaller gyrification index ($p=0.06$) than control infants.

Conclusions: Cortical cartography measures provide information on brain maturation and may be altered in infants with HLHS. In our current analysis there is only a trend towards altered cortical surface area and cortical folding. However, this is likely secondary to small sample size. Further investigation is warranted and currently under way with an additional five infants with HLHS. Establishing differences in cortical surface area and cortical folding may provide further understanding of the neurobiological basis of cerebral maturational delay in this population.

088 **Rachakonda, Tara, MD**

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Mentors: Judith EC Lieu, MD, MSPH; Joshua Shimony, MD, PhD

Diffusion tensor imaging in children with unilateral hearing loss

Rachakonda TD; Shimony JS; Lieu JEC

Introduction: Because children with unilateral hearing loss (UHL) have one hearing ear, it was thought that language acquisition proceeded normally in these children. However, these children score poorly on speech-language tests and have higher rates of educational and behavioral problems relative to those of their normal hearing peers. Diffusion tensor imaging (DTI) is used to detect microstructural damage in white matter (WM). This prospective, observational pilot study was conducted to observe differences in DTI parameters, such as fractional anisotropy (FA) and mean diffusivity (MD) in several structures in the brain between children with severe-to-profound UHL and their normal hearing (NH) siblings.

Methods: 16 children with UHL and 10 with NH underwent audiometry, IQ and oral language testing, and DTI. Parents provided demographic and educational data. The FA and MD of 8 regions of interest (ROIs) were sampled and averaged. Appropriate non-parametric tests provided statistical comparisons.

Results: Rightward FA asymmetries with corresponding FA asymmetries were seen regardless of hearing status in the centrum semiovale, Heschl's gyrus (gray and white matter), middle cerebellar peduncle (MCP) and posterior limb of the internal capsule; a leftward asymmetry was observed in the middle cingulate gyrus. No significant differences in DTI parameters were observed between the UHL and NH groups of children. Correlation analyses revealed significant relationships (Pearson $r = 0.5$) between cognitive scores and DTI parameters in the MCP and globus pallidus (GP).

Conclusions: DTI asymmetries between sides were observed regardless of hearing status. Changes in MCP and GP have been associated with attentional disorders; such changes may account for educational difficulties in children with UHL. These findings suggest that white matter microstructural patterns in several brain regions are preserved despite unilateral rather than bilateral auditory input.

No Poster Displayed

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Mentors: Terrie Inder, MD; Joan Luby, MD

Maternal psychosocial functioning, brain injury, and social and emotional development in very preterm children at age 2
Rogers C; Kidokoro H; Wallendorf M; Anderson P; Inder T

Introduction: Preterm birth is a significant public health problem associated with neonatal brain injury and social and emotional developmental delays. The aim of this study is to assess the impact of maternal psychosocial functioning on social and emotional development in a racially diverse cohort of very preterm infants with varying amounts of brain injury.

Methods: Forty infants (<30 weeks gestation) recruited from the Neonatal Intensive Care Unit at St. Louis Children's Hospital had an MRI at term-equivalent age. MR images were graded for severity of brain injury based on degree of white matter, gray matter, and cerebellar abnormalities. At age 2 years, mothers completed the Beck Depression Inventory-II and Parenting Stress Index-Short Form (PSI) and the Infant Toddler Social and Emotional Assessment (ITSEA). Maternal drug use was obtained from the clinical record and by self-report. Maternal psychosocial variables, socioeconomic status, and brain injury scores were entered into mixed effects regressions adjusting for gender and gestational age.

Results: Forty-three percent of the infants had moderate-to-severe brain injury. The percent of infants scoring at or above the 90^{th} percentile (at or below the 10^{th} percentile for Competence) were as follows: Competence – 45%, Externalizing – 23%, Dysregulation 15%, Internalizing 10%. Externalizing symptoms were associated with brain injury ($p<.05$), Total PSI scores ($p<.0001$), maternal drug use ($p<.01$), and lower SES ($p<.01$). Competence was associated with lower SES ($p<.05$) and total PSI scores ($p<.01$). Only total PSI score was associated with worse Internalizing ($p<.05$) and Dysregulation ($p< 0.0001$) symptoms. Maternal depression was not significantly associated with any ITSEA domain.

Conclusions: Among very preterm infants with substantial brain injury, maternal psychosocial factors and mother-child dyadic interactions are key factors that influence a child's social and emotional development. Neonatal follow-up programs and pediatricians should routinely assess for caregiver psychosocial functioning to aid in early identification, surveillance, and targeted interventions for the infants at greatest risk of poor social-emotional outcomes.

008 **Stoddard, Amy M, MD**
CRTC Postdoctoral Program
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Mentor: Jeff Peipert, MD, PhD

Fertility after IUD removal: The FAIR study
Stoddard A; Xu H; Madden T; Secura G; Allsworth JE; Peipert JF

Introduction: One of the main reasons clinicians do not recommend intrauterine devices (IUDs) to young women is the concern about future fertility. The objective of this study is to compare fertility rates at 12 months after contraceptive discontinuation in IUD users versus women discontinuing other methods.

Methods: This retrospective cohort study is a sub-study of the Contraceptive CHOICE Project (CHOICE) at Washington University in St Louis. Eligible participants are identified from the CHOICE database. Eligibility criteria include: 1) age 18-35, 2) sexually active with a male partner, 3) discontinuation of a contraceptive method to attempt conception; 4) English speaking; and 5) willing to comply with study protocol. The non-IUD group includes former pill, patch, ring and etonorgestrel implant users. Participants who have not yet conceived at the time of enrollment will continue to be followed via phone surveys at 6 months and 12 months after method discontinuation to see if they become pregnant.

Results: Thus far, we have enrolled 95 current and former CHOICE participants (61 IUD users and 34 non-IUD users). Overall the two groups have no statistically significant differences in baseline demographic characteristics. The mean age is 25.9 (SD 3.9) for IUD users, 24.4 (SD 4.0) for non-IUD users. Mean BMI is 26.7 (SD 7.1) for IUD users, 27.3 (SD 8.1) for non-IUD users. Both groups have similar proportions of white participants (63.9% vs 67.6%), current smokers (19.7% vs 17.6%) and history of gonorrhea/chlamydia (21.3% vs 20.6%). The IUD group has fewer nulliparous women than the non-IUD user group: 36.1% vs 55.9%, but this difference is not statistically significant ($p=0.06$). As of September 30, 2011, 39 out of 61 (63.9%) of IUD users have become pregnant compared to 23 out of 34 (67.7%) of non-IUD users.

Conclusions: We found similar pregnancy rates when we compared IUD users and non-IUD users discontinuing their contraceptive method to attempt conception. We will continue to follow study participants for 12 months after contraceptive discontinuation to further assess pregnancy rates, and will attempt to validate pregnancies and time to pregnancy with medical record reviews.

086 **Wineland, Andre M, MD**
CRTC Postdoctoral Program
Department of Otolaryngology, Washington University in St. Louis School of Medicine
Mentor: Jay Piccirillo, MD

Cognitive impact of tinnitus

Wineland AM; Pierce K; Piccirillo J

Introduction: Tinnitus, or ringing of the ear, affects nearly 50 million Americans and can be quite stressful. Approximately 10 million Americans will seek help for their tinnitus with common complaints of decrease energy, ability to concentrate and focus, and difficulty in recalling recent events.

Methods: Tinnitus participants were recruited through Washington University Otolaryngology Clinics from July 2009 to April 2011 and invited to participate in a full battery of standardized neurocognitive assessments. The group was divided based on the amount of "bother" they experienced as a result of having tinnitus. The amount of "bother" was captured through subjective (Global Bothersome Score) and objective (Tinnitus Handicap Index) measurements. Mild or non-bothersome tinnitus was quantitatively defined as having a Tinnitus Handicap Index (THI) less than 30; bothersome tinnitus was defined as having a THI score greater than 30. The two groups were compared against normative data provided in the testing materials.

Results: The two groups were different in age ($p<.001$), impact of tinnitus on sleep ($p=.001$), amount of effort exerted to ignore tinnitus ($p<.001$), and the amount of discomfort felt from tinnitus ($p<.001$). The bothersome group performed statistically worse on the Ruff 2&7, Stroop Color-Word, California Verbal Learning Test, and the Paced Auditory Serial Addition Test.

Conclusions: The amount of bother one experiences from their tinnitus appears to predict performance on the selected standardized neurocognitive tests. However, more sensitive tests need to be implemented to better assess the cognitive performance of these test as many of the results fall within the accepted range of "normal."

CRTC Predoctoral Program

047 **Abboud, Steven**
CRTC Predoctoral Program
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Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Christopher Carpenter MD
ISAR and TRST do not predict short-term adverse outcomes in geriatric patients
Abboud S; Carpenter C
Introduction: Acute exacerbations of chronic illnesses cause the geriatric adult to seek emergency medicine care at constantly increasing numbers. Mechanisms to focus finite resources on higher risk subsets would be of great value in this setting. Two instruments, the Identification of Seniors at Risk (ISAR) and Triage Risk Screening Tool (TRST) have been created to stratify seniors at higher risk for adverse outcomes such as death, institutionalization, functional decline, and ED revisit. Because both instruments have validity limited to the institutions they were created at, the National Institutes of Health has prioritized research of ISAR and TRST. Our objective is to validate and compare the prognostic accuracy of the ISAR and TRST for the composite outcome of one-month ED revisit, institutionalization, death, and functional decline.
Methods: This was a prospective, observational cohort study of consenting English speaking patients $\geq$ 65yrs old presenting to the Barnes Jewish Hospital ED in St. Louis MO between June 1 and July 31 2011. Patients $\geq$ 65 years old that did not live in a nursing home or > 30 miles from the hospital were screened using ISAR and TRST. Patient follow up was at 30 days post screening. Patients were evaluated for a correlation between ISAR and TRST score and the composite outcomes of 1) unscheduled ED visit or hospital admission 2) institutionalization, defined as admission to a nursing home or chronic care hospital or assisted living facility 3) death 4) functional decline defined as $\geq$ 3 point decline on 28 point OARS ADL.
Results: Among the 168 patients, the mean age was 74 years, 43.1% were men, and 62% were African American. Overall predictive values were summarized using ROC curves that yielded AUCs of 0.702 and 0.641 for ISAR and TRST respectively.
Conclusions: In the validation of both ISAR and TRST we found that both tests have poor predictive value for composite outcomes of ED revisit, institutionalization, death, and functional decline as indicated by unremarkable positive or negative LR's and the high proportion of patients identified as high risk. Future trials should evaluate these outcomes at 3 months and include ROC curves for each individual outcome.

No Poster Displayed

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Foundation for Anesthesia Education and Research
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Mentor: Peter Nagele, MD
Myocardial ischemia after electroconvulsive therapy
Bhat A; Nagele P
Introduction: Electroconvulsive therapy (ECT) is very commonly used to treat patients with severe major depression to gain an immediate improvement in their depressive symptoms. ECT involves the administration of a strong electrical current to the head of the patient and usually requires brief general anesthesia. The strong electrical current used in ECT initiates a generalized seizure in the patient that lasts for a few minutes. In spite of general anesthesia, ECT causes a major stress response in the patient and myocardial infarctions as well as myocardial damage after ECT have been reported. However, only scant data exist that systematically aimed to investigate the risk of myocardial ischemia after ECT.
Methods: A blood sample and EKG were obtained before and after an ECT treatment in patients electively scheduled for ECT. Samples were obtained from 3 ECT visits from each patient. To measure the extent of a potential myocardial injury, ultra-sensitive plasma troponin was measured, and the EKG interrogated for signs of myocardial ischemia.
Results: Preliminary results from 19 patients show that ECT was not associated with myocardial injury. The majority of patients had no detectable ultra-sensitive troponin in their blood (limit of detection < 3 pg/mL) and no ischemic changes in the EKG. In patients with a measureable baseline troponin, no change was observed after ECT.
Conclusions: Evidence from these preliminary data indicates that ECT is not associated with myocardial injury.

048 **Chang, Stephanie**

CRTC Predoctoral Program
St. Louis University School of Medicine
Mentor: Christopher Carpenter, MD

Self-rated health as a predictor of emergency department recidivism and functional decline among geriatric patients

Chang SK; Carpenter CR

Background: Numerous authors have found poor self-rated health (SRH) to be a significant risk factor for mortality and healthcare utilization, thus implicating SRH assessment as a useful clinical screening tool. This prospective cohort study seeks to determine whether SRH can predict functional decline and emergency department (ED) recidivism among geriatric patients, and to examine how cognitive impairment influences the predictive value of SRH.

Methods: Enrollment through consecutive sampling took place at one urban academic medical center in St. Louis, Missouri. Eligible patients were community-dwelling individuals 65 years of age and older, who presented to the study site ED during June and July 2011. SRH was assessed through a single question from the Quality of Life in Alzheimer's disease subject report, and the Short Blessed Test was utilized for cognitive screening. Information concerning ED recidivism and functional decline was collected through patient self-report, at 1 and 3 months following the index visit.

Results: As of August 30, 2011, 90 enrolled subjects have provided 1-month follow-up data. For the outcome of ED recidivism, sensitivity and specificity of poor/fair SRH was 38% (95% CI 11-72) and 38% (32-46) for cognitively normal patients, and 80% (48-96) and 36% (27-41) for cognitively impaired patients. For the outcome of functional decline, sensitivity and specificity of poor/fair SRH was 68% (49-84) and 52% (37-65 for cognitively normal patients, and 70% (53-86) and 35% (21-47) for cognitively impaired patients.

Conclusions: Preliminary analyses show that poor/fair SRH does not significantly predict ED recidivism or functional decline, among cognitively impaired or cognitively normal subjects. Identification of a useful triaging tool for elderly ED patients is needed, so that those at risk of adverse outcomes might be provided with appropriate interventions.

085 **Das, Sunil**

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Mentor: Jay Piccirillo, MD

Cognitive speed as an objective measure of tinnitus

Das SK; Kallogjeri D; Piccirillo JF

Introduction: Subjective, idiopathic tinnitus is a common but poorly understood condition for which no objective measurement or proven treatment exists. Tinnitus at least partially results from maladaptive cortical processes that cause a decline in cognitive performance, particularly in the domains of attention and processing speed. This study examined whether cognitive processing speed can be used as an objective tinnitus measure.

Methods: Participants with at least 6 months of subjective tinnitus were enrolled in this cross-sectional study. The Tinnitus Handicap Inventory (THI) captured the self-reported severity of tinnitus. Cognitive processing speed was objectively measured by the Brain Speed Test (BST). Scores from the BST were transformed into age-adjusted Z-scores using normative data. Co-existing functional somatic syndromes and depression were captured by the Whitely-7 and Patient Health Questionnaire-9 forms to assess their relationship with tinnitus severity measures. Additional neurocognitive tests were administered to validate BST results.

Results: 92 participants have completed the study. The median age was 53 (range 20-68), and most are white (91%). More than half (60%) are male, and 62% have a bachelor's or higher degree. Median tinnitus duration was 10 years (range 0.5-56 years) and 83% describe their Tinnitus Bother level as "*Bothered a Little*" or "*Bothered More Than a Little, but Not a Lot.*" Looking at all participants, a significant correlation did not exist between THI scores and BST Z-scores. However, a significant correlation between THI scores and BST Z-scores ($r=0.538$, $p<0.001$) did exist for the 59 participants with severe tinnitus (THI≥30). Secondly, significant correlations existed between BST z-scores and performance on the following standard neurocognitive tests: Stroop Color-Word T-Score ($r=-0.354$, $p=0.001$); PASAT 1.2 sec. Z-Score ($r=-0.35$, $p=0.001$); AQT color-form time ($r=0.464$, $p<0.001$).

Conclusions: Cognitive processing speed as defined by the BST can serve as an objective measure of the severity of chronic, subjective tinnitus. The BST will allow investigators to objectively stratify patients into severity groups and assess responses to investigational treatments.

031 **Escallier, Krisztina**

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CRTC Predoctoral Program
Cardiovascular Division
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Sharon Cresci, MD

Understanding phenotypic variability in hypertrophic cardiomyopathy

Escallier K; Bach RG; Cresci S

Introduction: Hypertrophic cardiomyopathy (HCM) is a complex genetic disease with a highly variable phenotypic progression. Occurring in 1/500 adults, most of HCM's nearly 1000 associated genetic mutations are inherited in an autosomal dominant pattern. However, even amongst patients with identical mutations, variable penetrance and disparate clinical manifestations of the disease are observed. The mechanism for this is not well understood. Currently, there is no way to predict if/when a HCM mutation-positive individual will develop the disease's characteristic hypertrophic changes or if they may progress to its more severe forms. These gaps in our knowledge base hinder clinicians' ability to provide genetic counseling or develop individualized management plans and also leave patients with great uncertainty. The aims of this study are to identify environmental and/or genetic modifiers/predictors of disease progression in HCM and to characterize the Midwestern HCM population.

Methods: This study is a longitudinal, prospective cohort study of men/women who are ≥15 YO and either (a) have been diagnosed with HCM, or (b) have a first-degree relative who has been diagnosed with HCM. HCM patients are sampled consecutively upon referral to Barnes Jewish Hospital/Washington University School of Medicine and are followed throughout their clinical course. Relatives undergo a research echocardiogram for evaluation of HCM. All subjects provide blood or saliva samples for DNA extraction and genetic analysis. Available demographic, echocardiographic, cardiac catheterization, surgical, and other data are collected for all subjects.

Results: Data collection and analysis are ongoing. This summer, we achieved our goal of rebuilding our database using new genetic study software that will allow for expanded data management and provide the capability of performing special pedigree analysis. We anticipate that our database will provide a strong foundation for analysis directed toward achieving our aims.

Conclusions: The identification of significant modifiers of clinical phenotype in HCM will allow for better determination of HCM prognosis and clinical management of the disease.

No Poster Displayed

Esguerra, Cybill R

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Department of Obstetrics and Gynecology, Washington University in St. Louis School of Medicine
Mentors: Jeffrey Peipert, MD, PhD; Gina Secura, PhD, MPH

Demographic and reproductive characteristics of young women ages 14 to 24 enrolled in the Contraceptive CHOICE Project

Esguerra CR; Peipert J; Secura G

Introduction: Rates of pregnancy and sexually transmitted infection among St. Louis teens consistently rank among the highest in the state, establishing them as significant local public health concerns. The purpose of this analysis was to describe the demographic characteristics, reproductive profiles, and sexual patterns of women ages 14 to 24 enrolled in The Contraceptive CHOICE Project and to compare women recruited at The SPOT to women recruited at other sites.

Methods: CHOICE is a prospective cohort study of 10,000 women investigating the effects of increased use of long-acting reversible methods of contraception (LARC) on unintended pregnancy rates. Responses (n=2720) from baseline interviews conducted upon enrollment into CHOICE were analyzed by age and recruitment site, focusing on The SPOT, a WUSM-affiliated clinic that provides free and confidential health services to St. Louis area youth. Recruitment sites were categorized into four groups: university-affiliated, community clinics, abortion clinics, and The SPOT. Statistical comparisons were made using χ^2 and Fisher's Exact tests for categorical variables.

Results: Results showed that The SPOT attracts a younger clientele (median age 19 compared to 21 for other groups). Despite this, women at The SPOT exhibit more high-risk behaviors, such as greater numbers of sexual partners, multiple simultaneous partners, and increased exposure to STIs. They have the least experience regarding contraception and demonstrate reluctance in talking about birth control with their sexual partners and health care providers. Conversely, women at The SPOT have the highest rates of STI testing, treatment, and counseling within the last year, which suggests at least a moderate level of access to the health care system.

Conclusions: Women who seek health services at The SPOT represent a high risk group with respect to risk of unintended pregnancy. Further studies investigating the efficacy of the youth-oriented clinic model exemplified by The SPOT in reaching and influencing reproductive and sexual health outcomes in high-risk populations are warranted.

135 **Gary, Julie J, MPH**

CRTC Predoctoral Program
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George Warren Brown School of Social Work, Washington University in St. Louis
School of Public Health, Saint Louis University
Mentor: William True, PhD

Predictors of quality of care in patients with cirrhosis and ascites

Gary JJ; Zeringue A; True W

Introduction: Ascites is the most common cirrhosis complication. Evidence based guidelines define standards of care in patients with cirrhosis and ascites. However, the extent to which patients with ascites meet these standards is largely unknown. We evaluated the quality of care in patients with cirrhotic ascites and factors associated with that care.
Methods: We conducted a retrospective cohort study of 781 patients with cirrhosis and ascites in 3 Veterans Affairs (VA) facilities between 2000 and 2007. Using an administrative and clinical database, we assessed quality of care as measured by seven indicators. We conducted a structured medical records review to explore patients' refusal, care outside the VA, or justifiable exclusions to certain care processes as explanations for non-adherence to indicators.
Results: Quality scores (max. 100%) varied across indicators, ranging from 30% for primary prophylaxis of bacterial peritonitis to 90% for testing the paracentesis fluid cell count and differential. Only 35.8% (95% CI, 32.5%-39.2%) of patients received all recommended care. Patients with more severe liver disease (as measured by Model for Endstage Liver Disease >20 *vs*. <14, odds ratio [OR] =1.68, 95% CI=1.12-2.50), no comorbidity (Deyo index 0 *vs*. $\geq$3, OR=2.39, 95% CI=1.36-4.22), or who lived closer to the hospital (< median *vs*. $\leq$ median distance, OR=1.54, 95% CI=1.1.0-2.15) received higher quality of care.
Conclusions: Health care quality, measured by receipt of recommended services, is suboptimal for cirrhotic ascites. The quality improves with increased disease severity but declines with the number of other chronic conditions. Most shortfalls in quality of ascites care remain unexplained.

118 **Gill, Bali**

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Mentor: Peter Nagele, MD

Myocardial ischemia after electro-convulsive therapy

Gill B; Nagele P

Introduction: Electroconvulsive therapy (ECT) is commonly used to treat patients with severe major depression to gain immediate improvement of their depressive symptoms. ECT involves administration of a strong electrical current to the patient's head and requires brief general anesthesia. The strong electrical current induces a generalized seizure that lasts for a few minutes. In spite of the general anesthesia, ECT causes a major stress response and myocardial infarctions as well as myocardial damage after ECT have been reported. However, only scant data exist that systematically aimed to investigate the risk of myocardial ischemia after ECT.
Methods: Venous blood samples and EKGs were obtained from patients electively selected for ECT before and after ECT for a maximum of 3 visits. Measurements of ultra-sensitive plasma troponin T and EKG examination for markers of myocardial ischemia were used to assess extent of myocardial damage.
Results: In preliminary data from 19 patients, a majority showed no detectable plasma ultra sensitive troponin (detection limit is < 3 pg/ml). Of those that had measurable plasma troponin, no change was seen after ECT. No myocardial ischemia was seen on EKGs.
Conclusions: Preliminary data indicates that ECT is not associated with myocardial injury.

099 **Hu, Jessie**

CRTC Predoctoral Program
Division of Emergency Medicine
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Christopher Carpenter, MD, MSc

The effect of cognitive dysfunction on patient comprehension of ED care among geriatric patients

Hu J; Carpenter CR

Introduction: The rate of geriatric patients in the ED has been steadily increasing over the past several years, and this trend is expected to continue with the aging baby-boomers. Approximately one third of older patients who are discharged will return to the ED within 14 days, with 90% presenting with the same problem that prompted the first visit, making it essential to identify factors which contribute to this population's high rate of unnecessary recidivism. Cognitive dysfunction in the elderly has been found to be associated with higher ED recidivism and lower patient satisfaction with ED care. The objective of this study is to assess the effect of cognitive dysfunction on comprehension of Emergency Department (ED) encounter among geriatric adults in four domains: (1) diagnosis, (2) tests and treatments in the ED, (3) prescriptions and follow-up recommendations, and (4) return instructions.

Methods: We conducted a cross sectional study on community-dwelling patients over the age of 65. Thirteen research assistants (RA) screened consecutive patients from June 1, 2011 to July 31, 2011 at the Barnes Jewish Hospital ED. The SBT, BAS, and cAD8 questionnaires were administered to assess cognitive function. At the time of discharge, patients were also asked to rate their subjective understanding and state the elements of their ED encounter for all four domains of ED care.

Results: We enrolled 165 patients. Around 47% of the patients perceived low comprehension in at least 1 domain of ED visit. Geriatric patients seemed to most often misunderstand elements of their ED care, such as tests and treatments received. Greater cognitive dysfunction was moderately correlated with self-rated lack of understanding of elements of ED care (Spearman $r = -.393$; $P < .01$). We anticipate greater cognitive dysfunction to also correlate with an actual lower understanding of ED care.

Conclusions: Cognitive dysfunction and in patients are significantly correlated with lower self-perceived comprehension of ED care. As baby-boomers age, more time and resources need to be allocated to help with patient comprehension, so that patients feel confident that they have an understanding of their health care.

112 **Janes, William E, OTD**

CRTC Predoctoral Program
Program in Occupational Therapy, Washington University in St. Louis School of Medicine
Mentors: Jack R. Engsberg, PhD; Carolyn M. Baum, PhD, OTR/L, FAOTA; Linda R. Van Dillen, PT, PhD

Alterations in shoulder biomechanics as a result of surgical decompression of peripheral nerves

Janes WE; Engsberg JR; Brown JM; Baum CM; Van Dillen LR

Introduction: Distal upper extremity nerve compression symptoms are thought to result in part from aberrant proximal kinematics. Although generally accepted, this causal relationship has never been tested. Examples from the lower extremity seem to suggest that distal neuropathy may be a precursor to altered proximal kinematics. The purpose of this study was to explore whether surgical relief of distal upper extremity neuropathies can lead to altered proximal kinematics. The specific aim of this project was to compare pre- and post-surgical kinematic data to identify any changes in shoulder biomechanics as a result of intervention.

Methods: Two persons with multi-level nerve compression syndrome were considered in a case-series format. Both were evaluated for neuropathy symptoms, proximal kinematic deficits, disability and quality of life before and six months after surgical decompression to correct distal neuropathy. Video motion capture data were collected during shoulder abduction, flexion, and scaption movements.

Results: Significant improvements were detected in scapulothoracic upward rotation and glenohumeral elevation (together, scapular rhythm) and scapulothoracic anterior tilt following surgery.

Conclusions: Nerve decompression surgery intended to correct distal neuropathy appears to result in improved proximal biomechanics. These findings suggest a more nuanced relationship between neuropathy and biomechanics than has been previously appreciated. This relationship may explain the general ineffectiveness of non-invasive treatment options for compression neuropathies. For a subset of patients, alleviating neuropathy symptoms may be a necessary precursor for improving proximal kinematics.

100 **Lai, Charlene**

CRTC Predoctoral Program
Division of Emergency Medicine
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Mentor: Christopher Carpenter, MD

Cost-benefit analysis of specialized screeners in the emergency department and of memory and aging project satellite intervention

Lai CW; Carpenter C

Introduction: Cognitive dysfunction is an expensive diagnosis that is increasing in the United States. The lack of health care providers able to correctly diagnose dementia creates a missed opportunity to decrease costs. The purpose of this study is to evaluate the costs and benefits of training screeners to detect cognitive dysfunction in older adults in the Emergency Department (ED) and the subsequent referral to the Memory and Aging Project Satellite (MAPS).

Methods: In a blinded, randomized controlled study at one urban academic medical center, screeners collected patients' responses to the Short Blessed Test (SBT). Consenting subjects were English-speaking adults>65 years who lived within 30 miles of St. Louis, MO. Subjects were excluded if deemed too ill to participate by the attending physician, institutionalized, and for those with cognitive impairment, lacked caregiver consent. Abnormally scoring subjects were referred to MAPS, a free community resource that offers memory testing and physician referrals. An abnormal result was defined as a SBT score>4. Follow-up phone calls to patients were made at a 1-month interval. Costs of ED visits, hospitalization, and institutionalization were found using the Medicare Expenditure Panel Survey, Healthcare Cost and Utilization Project, and National Health Expenditure Database. A decision analytic approach was used to analyze the data. One dimensional microsimulation and sensitivity analysis were used to test the robustness of the model and to identify critical uncertainties in the parameters.

Results: The prevalence of cognitive dysfunction in adults>65 in the ED was 52.8%. Assuming a 20% improvement in patient outcomes, screening and MAPS referral were shown to reduce the cost of patient care by $410. A 40% improvement in outcomes would reduce the cost by $714, and a 10% improvement by $105.

Conclusions: Preliminary analysis indicates that screening and MAPS referral reduces cost of patient care. Limitations of this study include generalizability, small sample size, accuracy of costs, and confounding variables such as socio-economic status, health literacy, and comorbidities.

123 **Lees, Katherine**

CRTC Predoctoral Program
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Mentor: Michael Avidan, MD

Intraoperative awareness, anesthetic management and BIS monitoring in right and non-right handed patients

Lees K; Rao S; Gradwohl S; Torres B; McNair P; Avidan M

Introduction: Intraoperative awareness is a rare complication with severe psychological consequences. The bispectral index (BIS) processed electroencephalogram monitor is approved for the measurement of anesthetic depth. Incorporating the BIS into anesthetic practice probably decreases the incidence of intraoperative awareness. Right-handed and non-right handed individuals reportedly have differences in anatomy and physiology of their brains. It is unknown whether non-right handed people have a different response to anesthetic agents, and the BIS has not been specifically evaluated in non-right handed people. We sought to determine if a difference in the intraoperative anesthetic management, BIS or intraoperative awareness exists based on patient handedness.

Methods: This was a pre-specified sub-study of the BAG-RECALL trial conducted at Washington University in St. Louis, University of Chicago and University of Manitoba. The study included 6041 patients who were at high-risk for intraoperative awareness. Data were collected from medical charts, intraoperative records and postoperative surveys.

Results: Gender was found to be significantly different between right and non-right handed patients (p = 0.006). No other patient characteristics, operative data or outcomes differed significantly based on handedness. The groups did not have significantly different BIS values (p = 0.760, 95% CI -0.955 - 0.697) or intraoperative intravenous anesthetic drug administration. The incidence of intraoperative awareness also did not differ significantly between right and non-right handed (p = 0.356, 95% CI -0.76% - 0.02%).

Conclusions: We did not find evidence that the incidence of intraoperative awareness is different in non-right handed patients. Based on our preliminary findings that there were no differences in BIS values during anesthetic maintenance between groups, no recommendation can be made about altering the management or monitoring of non-right handed patients during surgery. Our next step will be to create a linear mixed effects model to determine if the relationship between BIS and anesthetic concentration differs between right and non-right hand dominant individuals.

064 **Melson, Andrew T**

CRTC Predoctoral Program
Division of Emergency Medicine
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Richard Griffey, MD

The correlation between health literacy and numeracy in the emergency department

Melson A; Carpenter C; Griffey R

Introduction: Low Health Literacy is a well-known determinant of health outcomes that has been linked to increased emergency department usage and poor medication adherence. Although numeracy is often considered an important subset of health literacy, most commonly used health literacy screening tools do not incorporate a measure of numeracy. As little research has been done to establish a correlation between health literacy and numeracy, our aim was to explore this relationship in an emergency department (ED) setting.

Methods: We performed a prospective, observational convenience sample study of adult ED patients presenting from March - July 2011 to an urban, academic ED with 97,000 annual visits. We enrolled 262 patients with sub-acute illness and excluded patients with insurmountable communication barriers. Measurements of numeracy and health literacy consisted of 4 validated questions and 3 commonly-used screening tools (Short Test of Functional Health Literacy in Adults (S-TOFHLA), Rapid Estimate of Adult Literacy in Medicine-Revised (REALM-R), and Newest Vital Sign (NVS)) respectively.

Results: Numeracy performance was universally poor, with 11/262 subjects (4.2%, 95% CI 2.3, 7.5) correctly answering all questions, and a mean proportion of correct responses of 36.8%. Proportions of low or marginal health literacy as determined by the 3 screening tools varied significantly (S-TOHFLA: 20.2%, REALM-R: 49.6%, NVS: 75.6%, n=262 for all). However, correlation of each with health numeracy was low-to-moderate (S-TOFHLA: 0.416, REALM-R: 0.363, NVS: 0.499. $p<0.001$).

Conclusions: We observed varying degrees of health literacy but near-universal poor performance on numeracy testing. Correlations between numeracy and health literacy were low to moderate. Insofar as numeracy is considered a subset of health literacy, our results suggest that commonly used health literacy screening tools in ED-based studies inadequately evaluate and overestimate numeracy. This suggests the need for separate numeracy screening. Providers should be sensitive to potential numeracy deficits among those who may otherwise have normal health literacy.

038 **Millar, Melissa**

CRTC Predoctoral Program
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Mentor: Robert Figenshau, MD

Long term impact of laparoscopic cyst decortication in autosomal dominant polycystic kidney disease on renal function, hypertension, and pain control

Millar M; Haseebuddin M; Tanagho Y; Roytman T; Chen C; Clayman RV; Miller B; Desai A; Benway B; Bhayani S; Figenshau R

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenetic disorder of the kidney. Manifestation of the disease typically includes hypertension, chronic pain, and decreasing renal function. When conservative therapy fails to provide relief of chronic pain, surgical intervention may be indicated. We present our experience with long-term follow-up after laparoscopic cyst decortication (LCD) for ADPKD, focusing on factors predictive of progression to end-stage renal disease (ESRD).

Methods: Nineteen patients who underwent LCD between August 1994 and December 2003 with at least three-year follow up were included in this retrospective study. Mean follow-up was 10.85 years. Mean age at surgery was 44. Renal function was evaluated using the CKD-EPI creatinine-clearance (CrCl) formula. Patients who progressed to ESRD included those who underwent transplant, went onto dialysis, or were preparing for dialysis. Hypertension was evaluated using the anti-hypertensive therapeutic index (ATI), systolic and diastolic blood pressure. Pain assessment was based on narcotic use and on a telephone questionnaire.

Results: 67% report >50% improvement in pain after LCD and would readily repeat the surgery for pain control. 53% of patients had improved or stable ATI at last follow-up. A comparison of pre-op CrCl between patients who eventually developed ESRD and those who retain normal function reveals a lower pre-op CrCl in the former group. Lower pre-op CrCl was the only predictor of post-operative progression to ESRD.

Conclusions: Following LCD, durable relief of pain, but not hypertension control, is seen at ten years follow-up. Pre-op CrCl is a strong predictor of progression to ESRD following LCD. The role of LCD in altering the natural progression to ESRD in the subset of patients with compromised baseline renal function requires further investigation.

065 **Nadeem, Owais**

CRTC Predoctoral Program

Department of Internal Medicine, St. Louis University School of Medicine

Mentor: Christopher Carpenter, MD

The effect of health literacy on patient comprehension of ED Care among geriatric patients

Nadeem O; Carpenter C

Introduction: The objective of this study is to assess the effect of health literacy on comprehension of Emergency Department (ED) encounter among older adults for four domains: (1) diagnosis, (2) tests and treatments in the ED, (3) prescriptions and follow-up recommendations, and (4) return instructions.

Methods: We conducted a cross sectional study of 165 adults, over the age of 65 years, English-speaking, community dwelling patients. Thirteen research assistants (RA) covered screening consecutively from June 1, 2011 to July 31, 2011 at the Barnes Jewish Hospital ED. Exclusion criteria included failure to consent, residence more than 30 miles away, residence in a nursing home, non-English speakers, patients who emergency physicians judged to be too critically ill to participate and patient refusal to give consent. The RA's administered "Rapid Estimate of Adult Literacy in Medicine-Short Form" (REALM-SF) to assess health literacy. At the time of discharge, patients were also asked to rate their subjective understanding of their ED encounter for all four domains of ED care.

Results: Around 47% of the patients demonstrated a comprehension deficiency in at least 1 domain of the ED visit. This deficiency was 81% among patients with less than 9^{th} grade reading level and 23% among patients with greater than 9^{th} grade reading level. The deficits were most common for the domain category of ED care. Health literacy had a statistically significant effect on patient comprehension of ED care, specifically for patients with normal cognition.

Conclusions: Many patients do not understand their ED care or their discharge instructions. Moreover, health literacy is significantly associated with limited comprehension of ED care.

056 **Obermann, Karen**

CRTC Predoctoral Program

Department of Internal Medicine, Washington University in St. Louis School of Medicine

Mentors: Catherine M Roe, PhD; John C Morris, MD

Effects of 100 commonly used drugs and supplements on cognitive performance in older adults

Obermann KR; Roe CM; Morris JC

Introduction: There are conflicting reports regarding the effects of medications on cognition in older adults, and overall there is a lack of evidence-based data involving drugs and cognitive performance in this population. The specific aim of the study is to determine if use of common medications is associated with increased or decreased performance on psychometric tests.

Methods: Cross-sectional analysis was done on archival data from the National Alzheimer's Coordinating Center Uniform Data set. The 100 most-commonly-used drugs and supplements were determined by creating a frequency table for the study population. Participants were age 50 years or older and cognitively normal (N=6352). Composite scores were constructed from 10 psychometric tests and general linear models adjusting for age, sex, race, and education were used to test whether the mean composite score differed for participants taking and not taking each of the top 100 medications.

Results: Fifteen medications showed a significant ($P<0.05$) difference in mean psychometric composite scores. Use of alendronate, ibuprofen, and loratadine was associated with increased psychometric performance. Use of potassium chloride, metformin, clopidogrel, ubiquinone, esomeprazole, rosuvastatin, ranitidine, ferrous sulfate, tramadol, pyridoxine, lorazepam, and alprazolam was associated with decreased psychometric performance.

Conclusions: Use of common medications is associated with cognitive performance in older adults. Future studies will examine longitudinal effects of medications on cognition and cognitive reserve.

106 **Padhye, Leena V**

Medical Student
CRTC Predoctoral Program and Dean's Fellowship
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Washington University in St. Louis School of Medicine
Mentors: Gregory P. Van Stavern, MD; Aseem Sharma, MD

Correlation of visual parameters and papilledema neuroimaging features, and the reversibility of papilledema neuroimaging features

Padhye LV; Van Stavern GP; Sharma A

Introduction: Papilledema refers to optic disc swelling resulting from high intracranial pressure (ICP). The precise mechanism by which papilledema occurs remains uncertain. Although orbital neuroimaging features associated with papilledema are well-described, it is unclear whether these findings correlate with visual function. Idiopathic Intracranial Hypertension (IIH) is a condition in which the intracranial pressure is elevated with no obvious cause, causing papilledema and visual loss. A primary goal of treatment in IIH is to prevent disabling visual loss, but there is a lack of strong evidence guiding clinical management decisions. The utility of papilledema neuroimaging findings as a surrogate marker for visual loss, or a predictor of visual loss, is understudied. This retrospective cross-sectional review aims to correlate parameters of visual function with orbital magnetic resonance imaging (MRI) findings, and to assess the reversibility of specific imaging features.

Methods: The patient visual parameters of papilledema grade, visual field mean deviation, visual acuity, and color vision were correlated with specific neuroimaging features, including optic nerve thickness, optic nerve sheath thickness, cerebrospinal fluid space around the optic nerve, optic nerve head appearance (globe configuration and enhancement), sellar configuration, ventricular appearance, sulci appearance, and venous anatomy (when applicable).

Results: Data analysis is ongoing. We anticipate that the severity of the papilledema correlates with the severity of the neuroimaging findings.

Conclusions: The results of this study may help guide clinicians when making clinical management and treatment decisions for patients with IIH in particular, and papilledema in general. Investigating the reversibility of common papilledema MRI features may lead to insights into the mechanism of papilledema, which could ultimately also lead to better management of the disease.

129 **Peterson, Daniel, MS**

CRTC Predoctoral Program
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Mentor: Gammon Earhart, PT, PhD

Relationship between bilateral coordination of steps and FOG in people with PD

Peterson DS; Plotnik M; Hausdorff J; Earhart G

Introduction: 50% of those with Parkinson disease (PD) experience freezing of gait (FOG), described as an inability to produce effective steps. FOG is a disabling symptom of PD, directly related to falls and reduced quality of life. FOG has been suggested to be related to bilateral coordination of steps during gait; however, coordination has only been measured during forward walking. Determining how coordination is affected by tasks which more frequently elicit FOG, such as turning or backward walking, is critical to understand the relationship between coordination and freezing. Therefore, the goal of this study was to further determine the relationship between FOG and coordination by measuring how tasks related to FOG affect coordination of steps during gait.

Methods: Ten people with PD who do freeze "freezers", 18 who do not freeze "non-freezers", and 10 age-matched healthy adults completed forward walking and tasks related to freezing (turning and backward walking). Bilateral coordination of steps, measured as Phase Coordination Index (PCI) was calculated for all tasks. Severity of PD and FOG were quantified for those with PD.

Results: No differences in disease severity or duration were observed between freezers and non-freezers ($p=0.2$ and 0.8, respectively). A group effect was, however, noted ($F_{2,35}=14$; $p<0.001$) such that freezers exhibited the worst coordination, followed by non-freezers, and healthy controls. Tasks associated with FOG (turns and backward walking) resulted in worse coordination with respect to forward walking ($F_{2,22}=48$; $p<0.001$), and this effect was most pronounced in freezers ($F_{4,72}=3.4$; $p=0.01$). Coordination across tasks was positively correlated to severity of freezing ($p=0.004$) such that worse coordination predicted worse severity of freezing.

Conclusions: These data provide support for the hypothesis that bilateral coordination of steps is related to FOG. Understanding factors related to FOG may help to elucidate mechanisms underlying freezing. Further, FOG is particularly difficult to elicit in laboratory and clinical settings. Identifying quantifiable variables, such as PCI, which are associated with FOG could help identify individuals at risk for FOG, and track the progression of this symptom.

023 **Reagan, Mary**

CRTC Predoctoral Program
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Mentors: Jeffrey Peipert, MD, PhD; Gina Secura, PhD

STEPS: Study to Evaluate Male Partner Screening

Reagan M; Secura G; Peipert J

Introduction: Controlling sexually transmitted diseases (STDs), such as infection with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC), is a serious public health challenge. Routine screening for these STDs is largely directed at women because of the severity of sequelae associated with female infection. Despite these screening efforts, infection rates continue to rise. In order to improve infection rates, screening must successfully target the large reservoir of infected men. The purpose of this study is to establish recruitment methods for a clinical trial of male STD screening.

Methods: Male participants were randomized to either home or in clinic urine-based STD screening. Passive brochure distribution was employed to recruit men for the first 13 months of the study. After 13 months, active field recruitment was implemented. Active field recruitment consisted of study advocates personally presenting the study to eligible men in areas of participants' residences. Monthly enrollment rates were examined and participant characteristics were compared between recruitment methods.

Results: Between June 2010 and July 2011, 4,436 brochures were distributed. This resulted in the enrollment of 67 men (rate = 5 men per month). Active field recruitment yielded 133 men enrolled between July 2011 and September 2011 (rate = 66 men per month). Preliminary data showed that men enrolled by active field recruitment were significantly older (32 vs. 27, $p<0.01$). Race, previous STDs, number and gender of sex partners, and condom use were similar between groups ($p>0.05$).

Conclusions: Recruiting men into a STD screening trial is feasible. The most effective outreach method is to physically approach men in the communities where they live. Brochure distribution is not an efficient way to recruit men to be screened.

No Poster Displayed

Ruparelia, Beejal

CRTC Predoctoral Program
Division of General Medical Sciences
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Brian F Gage, MD, MSc

The effect of the CYP 4F2 V433M polymorphism on maintenance warfarin dosing: a meta-analysis

Ruparelia B; Lai J; Venker B; Moskowitz G; Eby C; Gage, BF

Introduction: Warfarin inhibits the regeneration of Vitamin K_1H_2, thereby inhibiting the synthesis of clotting factors to prevent thrombosis. While VKORC1 and CYP 2C9 gene polymorphisms are well-established as warfarin dose predictors, only 53-54% of warfarin inter-patient variability is known. Studies have investigated the role of the CYP 4F2 V433M polymorphism (rs2108622) for association with an increase in warfarin dose, but results are conflicting and inconsistent. Our objective was to systematically integrate the conclusions of these studies to determine the true effect of the V433M polymorphism on warfarin dose.

Methods: We conducted a search of published literature using Embase, PubMed, and Google Scholar. Three reviewers extracted data from each study twice to obtain the primary outcome variable: percent increase in mean weekly warfarin dose. We then conducted a meta-analysis using DerSimonian-Laird's random effects model.

Results: Twenty studies were identified according to eligibility criteria. With analysis of 10 of the 20 studies, we have found a 5.6% (with a 95% CI of 3.5-7.6%) increase in mean weekly warfarin dose. We expect the increase in mean weekly warfarin dose to be consistent with these results upon completed analysis of all studies.

Conclusions: Though our review is incomplete, the current 5.6% increase in warfarin dose helps to validate the significance of genotyping for the CYP 4F2 V433M polymorphism (rs2108622) in conjunction with VKORC1 and CYP 2C9 genotyping. Since CYP 4F2 activity is not a major pathway in anticoagulation, the effect of the V433M polymorphism is expected to be moderate as demonstrated. These results have the potential to offer better predicted therapeutic warfarin doses, preventing warfarin-related adverse events and minimizing costly hospital readmissions. Thus, a cost effective analysis is needed to determine the economic implications of genotyping for this polymorphism.

No Poster Displayed

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Mentor: Michael N Diringer, MD

Effect of osmotic agents on cerebral blood flow in traumatic brain injury

Scalfani MT; Dhar R; Zazulia AR; Videen TO; Diringer MN

Introduction: Patients with traumatic brain injury (TBI) are at risk for secondary ischemic neurological injury initiated by cerebral edema causing increased intracranial pressure (ICP). Elevated ICP can critically reduce cerebral perfusion pressure (CPP) and threaten adequate cerebral blood flow (CBF). We sought to determine if improving CPP (by lowering ICP) with osmotic agents led to a rise in CBF in patients with severe TBI and intracranial hypertension; specifically whether osmotic therapy could reverse regional reductions in CBF to hypoperfused or injured tissue.

Methods: A convenient sample of eight adult TBI patients (five with focal injuries) were treated with 1 g/kg 20% mannitol or 0.686 ml/kg 23.4% saline. CBF was measured with ^{15}O-PET imaging before and 1 hour after treatment globally as well as in regions with contusion or edema (focal injury, defined by co-registered CT) and regions with baseline CBF < 25 and < 20 ml/100g/min (hypoperfused regions).

Results: Following treatment, ICP fell from 22.4±5.1 to 15.7±7.2 mm Hg (p=0.007) and CPP rose from 75.7±5.9 to 81.9±10.3 mm Hg (p=0.03). There was a trend for global CBF to rise from 30.9±3.7 to 33.1±4.2 (p=0.07). In regions with focal injury, baseline flow was 25.7±9.1 and rose by 6.2% (p=0.42). However in regions with baseline CBF < 25 (104 of 677 total regions), CBF increased by 20% from 18.6±5.0 to 22.4±6.4 (p < 0.001) after osmotic therapy. CBF also rose by 24% in hypoperfused regions with CBF < 20 at baseline (p <0.001). After treatment, the number of regions with CBF < 25 and < 20 ml/100g/min decreased by 40% and 43% respectively (p <0.001).

Conclusions: Osmotic agents, in addition to lowering ICP, also improved CBF to hypoperfused regions in patients with TBI, potentially salvaging vulnerable brain tissue from ischemic injury.

No Poster Displayed

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Mentor: Michael N Diringer, MD

Osmotic agents lower ICP independently of reducing CBV

Scalfani MT; Diringer MN

Introduction: The mechanism by which osmotic agents such as mannitol and hypertonic saline reduce cerebral edema and intracranial pressure (ICP) has not been fully elucidated. There are two proposed mechanisms by which this reduction in intracranial volume occurs: by reducing brain cellular and interstitial water content or by reducing cerebral blood volume (CBV). We sought to determine if mannitol or 23.4% saline (HS) acutely lowered CBV and how their response differed in a series of patients with severe brain injury who were receiving osmotic therapy to treat intracranial hypertension or cerebral edema.

Methods: Subjects were randomized to receive an equi-osmolar dose of mannitol (1 g/kg) or HS (0.686 ml/kg). PET measurements of global CBF, CBV, oxygen extraction fraction (OEF) and cerebral metabolic rate for oxygen ($CMRO_2$) were performed before and 1 hour after receiving osmotic therapy. At the time of each image acquisition, physiological data were recorded. Statistical analysis was performed using 2-tailed paired t-tests and repeated measures ANOVA to compare mannitol versus HS.

Results: 21 patients with traumatic brain injury (n=8), large hemisphere stroke (n=9) and intracerebral hemorrhage (ICH, n=4) were studied. Baseline physiologic data were similar in both treatment groups. Blood pressure did not change after osmotic therapy in either group. In the subset who had ICP monitoring, ICP fell (22.3±4.4 to 14.8±6.5 mm Hg, p=0.001) and CPP rose (83.4±16.6 to 89.7±17.9 mm Hg, p=0.01). Osmotic therapy resulted in an increase in CBV (3.4±0.8 to 3.7±1.0 ml/100g, p=0.03) which was evident in the mannitol group (n=13) (3.6±0.7 to 4.0±1.0, p=0.04) but not in the HS group (n=8) (3.1±0.8 to 3.2±0.8, p=0.537). Similarly CBF increased in the mannitol group (34.0±11.3 to 37.2±16.6 ml/100g/min, p=0.04) but not in the HS group (32.8±14.6 to 33.9±13.4, p=0.61). There were no significant differences between mannitol and HS.

Conclusions: Neither mannitol nor 23.4% saline lower CBV indicating that the observations made in experimental studies do not translate into the clinical area. Another mechanism such as a reduction in brain water may better explain their ability to lower ICP.

No Poster Displayed

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Mentors: Jeffrey F Peipert, MD, PhD; Gina M Secura, PhD, MPH

The study to evaluate male partner screening (STEPS): Preliminary results

Shih, SL; Secura GM; Peipert JF

Introduction: In the U.S., there are currently no recommendations for or against the screening of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (GC) infections in men. Previous studies in women have shown home-based screening approaches for CT/GC to lead to higher response rates than traditional clinic-based screening methods. The purpose of this study is to determine whether home-based urine testing, as compared with clinic-based testing, is a more acceptable and effective approach for CT/GC screening in men.

Methods: A randomized controlled trial was conducted to compare the return rates of completed test kits for men who were randomized to home-based screening (n=100) to those who were randomized to clinic-based screening (n=100). Participants were English-speaking men between the ages of 18-45 years who resided in St. Louis, and were recruited via brochure distribution and active field recruitment.

Results: Of the 200 men randomized, 92% (n=184) have completed the trial (n=94 home vs. n=90 clinic). Preliminary results suggest that there were no statistically significant differences in baseline demographic or sexual history characteristics between the home and clinic groups. However, there was a trend towards the home screening group having more Black participants (73% vs. 64%, p=0.38) and less than a college education (56% vs. 46%, p=0.37). Overall, 59% (n=108) of participants completed testing, including 69% (n=65) of men assigned to home screening compared to 48% (n=43) of those assigned to clinic screening. After adjusting for race and education, home screening was found to be approximately 50% more effective than clinic screening (RR_{adj} 1.51, 95% CI 1.18-1.94).

Conclusions: Our results suggest that home-based urine testing is a feasible, acceptable, and effective approach to screening for sexually transmitted infections in men. Home-based screening may be a good adjunct to current clinic-based approaches to sexually transmitted infection screening.

107 **Sorensen, C J, MS**
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Mentor: LR Van Dillen, PhD

Validity of a model for low back pain symptom development during prolonged standing

Sorensen CJ; Van Dillen LR

Introduction: Jobs requiring prolonged standing are associated with increased risk of low back pain (LBP). Studies using a laboratory-based paradigm in which people perform simulated work tasks while standing for a 2-hr period have shown that ~50% of back-healthy people develop LBP symptoms. It is currently unknown if the LBP symptoms developed during the standing paradigm are similar to those reported by people with clinical LBP and if back-healthy people who develop LBP symptoms are at increased risk for future episodes. The purposes of this study were to compare symptoms and 2) during standing between LBPs and back-healthy people who develop LBP.

Methods: LBPs reported the location and quality of their typical symptoms on a body pain diagram (BPD). Both LBPs and back-healthy people then participated in the paradigm. Every 15 minutes people reported the quality and location of symptoms on a BPD and intensity of LBP symptoms on a 100 mm visual analog scale (VAS). Healthy people were considered pain developers (PD) if they had an increase of ≥ 10 mm on the VAS.

Results: The location of typical symptoms was reproduced in all LBPs during standing. 78% of typical symptoms were reproduced in LBPs during standing. The majority of symptoms were described as aching, stiffening, tightness and cramping for both LBPs (77%) and PDs (88%). The location of symptoms in PDs was the same as in LBPs for all but one subject. Maximum VAS scores (LBPs=46±17; PDs=24±9) and change in VAS scores (LBP=35±10; PDs=22±9) during standing was greater for LBPs than PDs.

Conclusions: Location and quality of LBP symptoms during the standing paradigm were similar to those reported as typical by LBPs and similar between LBPs and PDs. Symptom intensity was higher and change in intensity was greater for LBPs than PDs in standing. These preliminary data support the validity of the prolonged standing model for the study of LBP in the laboratory.

089 **Thaker, Aditya S**

CRTC Predoctoral Program
St. Louis College of Pharmacy
Mentor: Mario Castro, MD, MPH

Reslizumab in poorly controlled eosinophilic asthma: the link between asthma control and short-acting bronchodilator usage

Thaker A; Castro M

Introduction: Asthma is a chronic disorder characterized by reversible airway constriction and inflammation upon exposure to an "antigen." Eosinophilic asthma is a severe phenotype in which excessive eosinophils are found in the airways and release mediators responsible for airway remodeling and fibrosis. Interleukin-5 (IL-5) recruits eosinophils to airways and activates eosinophils to release mediators. Anti-IL-5 monoclonal antibodies (reslizumab) have shown to improve asthma control, pulmonary function, and lower eosinophils in a clinical trial. We aim to evaluate reslizumab impact on asthma control as reflected by short-acting "rescue" bronchodilator usage.

Methods: We designed a secondary data analysis that looked at patient responses in the Asthma Control Questionnaire (ACQ) from the clinical trial. Our primary outcome was patient reported rescue inhaler use. Secondary outcomes include patient reported symptoms of shortness of breath and wheezing. Sub-analysis of data was done based upon the presence of nasal polyps. Statistical analysis was done using analysis of covariance (ANCOVA).

Results: We found no differences in rescue inhaler use (mean reduction in ACQ score in reslizumab group was -0.3 and in placebo was -0.1, p=0.5311). Patients who had nasal polyps did see a reduction in rescue inhaler use (-0.6 in reslizumab group and +0.5 in placebo, p=0.0197). We also did not find statistical significant differences in symptoms of shortness of breath (mean reduction in ACQ score for reslizumab group was -0.8 and in placebo was -0.3, p=0.0542) and wheezing (mean reduction in ACQ score for reslizumab group was -1.0 and in placebo was -0.5, p=0.0841).

Conclusions: Overall, no link could be established between asthma control and rescue inhaler use between reslizumab and placebo. Further studies involving reslizumab are needed to evaluate its impact asthma control.

126 **Tran, Irene**

CRTC Predoctoral Program
Program in Physical Therapy, Washington University in St. Louis School of Medicine
Mentor: Susan Racette, PhD

Physical activity in school children: indoor versus outdoor recess and a multi-component intervention

Tran IT; Clark BR; Racette SB

Introduction: The Missouri Department of Elementary and Secondary Education requires a minimum of 150 minutes of physical activity per week for elementary students. Daily recess, 20 minutes in length, can count for 100 minutes of the state-mandated physical activity requirement. There are limited data that quantify physical activity in youth during indoor and outdoor recess. The aims of this project were: 1) to evaluate physical activity in urban students during outdoor and indoor recess and 2) to evaluate a recess intervention.

Methods: This prospective cohort study involved students in grades 2-5 attending urban public schools (n = 106; 49 boys, 57 girls). 32% were categorized as overweight or obese. Physical activity was assessed using uni-axial accelerometer pedometers during recess in 3 settings: outdoors, indoor gym, and indoor classroom (determined by weather and school policy). An 8-week, multi-component recess intervention was delivered outdoors and in the gym. The intervention included hip-hop dance, structured activities (e.g., football, kickball) and provided recess equipment (e.g., jump ropes, Frisbees). Assessments were made twice weekly in all three settings at baseline, mid-study, and end-of-study. Data were analyzed using mixed model factorial analysis of variance with adjustment for grade, sex, school, and weight status.

Results: Students achieved the greatest amount of physical activity during outdoor recess (1147 ± 50 steps per recess period, $p < 0.001$); indoor recess in the gym enabled more activity than indoor recess in the classroom (784 ± 70 vs. 270 ± 64 steps, $p < 0.001$). Although students participated in a variety of the provided recess activities, the intervention did not have a significant effect on physical activity when controlling for recess setting. Males were more active than females (845 ± 45 vs. 622 ± 41 average steps, $p < 0.001$).

Conclusions: Results suggest that it is important for schools to provide outdoor recess to maximize physical activity of students. When indoor recess is necessary, an open gym is superior to a classroom.

067 **Turner, Kanika**

CRTC Predoctoral Program
Division of Emergency Medicine
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Christopher R. Carpenter, MD

Evaluation of the Montreal Cognitive Assessment screening tool for use in urban aging African Americans who present to the emergency department

Turner KA; Carpenter CR

Introduction: Mild cognitive impairment (MCI) is a transitional state between normal aging and dementia with preserved activities of daily living. Detecting MCI in aging adults who present to the Emergency Department (ED) is critical for prevention and treatment of dementing illnesses. Additionally, disparities in cognitive impairments exist between aging African Americans (AA) and Caucasian Americans (CA). The Montreal Cognitive Assessment (MoCA) is a screening tool used to detect MCI. The purpose of this study was to evaluate and compare the diagnostic accuracy between AA and CA of the MoCA in an ED setting for detection of MCI.

Methods: This was a cross sectional, consecutive sampling study. Eligible subjects were consenting English-speaking community dwelling patients over age 65. Exclusion was based on ED physician judgment, caregiver's refusal, or residence >30 miles from hospital. Trained researchers administered the Brief Alzheimer's Screen (BAS), Short Blessed Test (SBT), AD8, and MoCA. MCI was defined as a MoCA score <26. Chi-square analyses were performed with MoCA scores. Diagnostic accuracy of the BAS, SBT, and AD8 to detect MoCA-defined MCI was assessed using SPSS.

Results: We enrolled 165 patients: 61% AA, mean age 74 years, 39% with < 12th grade education, and 57% female. MCI was detected in 85% of patients who completed the MoCA with 97% MCI incidence in AA and 66% in CA.

Conclusions: The MoCA is not an ideal MCI-screening instrument in the ED. The incidence of MCI as judged by the MoCA is unacceptably high and likely an epiphenomenon reflective of the difficulty of administering the test in ED settings, particularly for AA, but also for CA. Since this was a pilot study, further research is needed to develop better screening tools for AA and CA who present to the ED.

058 **Venker, Brett**

CRTC Predoctoral Program
General Medical Sciences Division
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentor: Brian Gage, MD

Safety and efficacy of new anticoagulant drugs for the prevention of venous thromboembolism after hip and knee arthroplasties

Venker B; Gage B

Introduction: The incidence of venous thromboembolism (VTE) in patients undergoing hip and knee arthroplasties is high despite new therapies being available. Dabigatran, apixaban, fondaparinux, and rivaroxaban are new anticoagulants that may show promise for VTE prevention in this patient population. The purpose of this study was to determine which new anticoagulant drug has the best safety and efficacy outcomes for VTE prevention in hip and knee arthroplasty patients.

Methods: We searched Pubmed (including Medline), Embase, and Clinicaltrials.gov to find randomized controlled trials of these anticoagulants. We used Dersimonian-Laird's random-effects model to combine studies using similar regimens.

Results: The relative risk (RR) of VTE plus death varied from 0.52 to 1.20 for the new anticoagulants compared to enoxaparin. The RR was lowest for rivaroxaban 10 mg/day and fondaparinux 2.5 mg/day and highest for dabigatran 150mg twice daily. The RR of major/clinically relevant bleeding was also measured but excluded fondaparinux due to insufficient data. Values ranged from 0.84 to 1.32. Apixaban 2.5 mg twice daily had the lowest RR of bleeding, while rivaroxaban the highest. Apixaban was the only drug to have a RR less than one for both bleeding and VTE.

Conclusions: With the possible exception of apixaban, new anticoagulants (at clinically tested doses) that lower the risk of VTE, raise the risk of bleeding, and new anticoagulants that lower the risk of bleeding, raise the risk of VTE.

138 **Vu, John, MPH**

CRTC Predoctoral Program

Department of Otolaryngology, Washington University in St. Louis School of Medicine

Mentors: Gregory Sayuk, MD, MPH; Jay Piccirillo, MD, FACS; Beau Ances, MD, PhD

Exploration of cortical neural network abnormalities in irritable bowel syndrome (IBS)

Vu JT; Sayuk GF; Piccirillo JF; Ances BM

Introduction: Irritable bowel syndrome is highly prevalent in American society. Yet, after four decades of research, the proposed mechanisms explaining its pathophysiology remain disappointingly insufficient. The inability of studies of the periphery (bowel and its enteric nervous system) to sufficiently explain IBS may derive from the importance of the central nervous system (CNS) to IBS pathophysiology. This cross-sectional pilot study seeks to determine whether patients with IBS have abnormalities within the resting-state cortical neural networks responsible for sensory integration, attention, cognition, and introspection and whether the number or severity of somatic symptoms are associated with the degree of abnormalities in those connections.

Methods: This study is a cross-sectional pilot research project. We stratified enrollment to ensure approximately equal numbers of mild, moderate, and severely bothered IBS patients based on responses to IBS-SSS, a validated IBS-specific severity rating scale. Each subject received an fcMRI using a sequence validated at Washington University. Each IBS patient was matched to a control by age, gender, and handedness. In addition to the fcMRI, enrolled participants completed a battery of validated patient self-report questionnaires exploring 1) the presence of physical, functional, and cognitive impairments, 2) the presence and severity of mood and anxiety disorders, and 3) the presence and severity of medical comorbidities. Participants also completed 1) questionnaires exploring factors for the development and maintenance of IBS and 2) one objective measure of cognitive processing speed – *Brain Speed Test.*

Results: We have recruited and scanned 20 IBS patients and 11 age-matched controls (resting state fcMRI). We have obtained the fcMRIs of 9 healthy volunteers from other studies using the same fcMRI sequence and have performed the same questionnaire based assessment and computer based testing on these patients. Post processing of these fcMRI's is currently in progress.

Conclusions: fcMRI processing is currently in progress.

No Poster Displayed

Yom, Victoria

Medical Student

CRTC Predoctoral Program

Department of Ophthalmology & Visual Sciences, Washington University in St. Louis School of Medicine

Mentors: Anjali Bhorade; Mae Gordon, PhD

On-road driving performance in moderate and advanced glaucoma patients

Yom VH; Lee AY; Dewan VN; Carr DB; Barco PP; Wilson BS; Gordon MO; Bhorade AM

Introduction: Although it is known that glaucoma patients have a higher rate of motor vehicle collisions than individuals without glaucoma, only a few relevant studies have used the gold standard of on-road testing to assess driving performance in glaucoma patients. This study compared on-road driving performance in patients with moderate and advanced glaucoma to age-matched normal controls, using the validated modified Washington University Road Test (mWURT).

Methods: Glaucoma patients ages 55 years and older with moderate and advanced glaucoma based on the Glaucoma Staging System and a visual acuity of 20/70 or better in the better-seeing eye and age-matched normal controls were enrolled. Inclusion required participants to be currently driving with a valid driver's license and no major comorbidities or medications that impair driving. Participants completed the mWURT, an on-road driving evaluation conducted by a masked, certified driving instructor over a 12-mile route through residential and business areas in St. Louis, MO. The driving instructor scored overall driving performance as pass, marginal pass (requiring restrictions or training), or fail and recorded the number of at-fault critical interventions (brake and/or steering intervention) required during the course. A Fisher's exact test was performed to compare overall driving performance and the number of critical interventions required between glaucoma participants and normal controls.

Results: Nineteen glaucoma (70.6 ± 7.2 years) and 39 normal (70.9 ± 8.4 years) participants completed the evaluation. Eight of 19 (42%) glaucoma participants either marginally passed or failed compared to 8 of 39 (21%) normal controls (Fisher's exact test, p=0.12). The difference in the proportion of glaucoma participants and normal controls who marginally passed or failed was 21% (95% CI, -2% to 47%). Three of 19 (16%) glaucoma participants required 2 or more total critical interventions compared to 0 of 39 (0%) normal controls (Fisher's exact test, p=0.031).

Conclusions: A substantially higher proportion of patients with moderate and advanced glaucoma marginally passed or failed the on-road driving evaluation or required more than one critical intervention compared to individuals without glaucoma. The true difference in the ability to marginally pass or fail the driving test between glaucoma participants and normal controls could be as great as 47%. Results from this ongoing study may help identify aspects of vision associated with unsafe driving maneuvers in glaucoma patients.

David F. Silbert Summer Fellowship

114 **Chen, Sara**
Medical Student
David F. Silbert Summer Fellowship Award
Summer Research Program
Department of Molecular Oncology, Washington University in St. Louis School of Medicine
Mentor: Katherine Weilbaecher, MD
Role of *Smoothened* inhibitors on osteoclast activity in bone metastasis
Chen SX; Heller E; Hurchla MA; Xiang J; Schneider J; Joeng KS; Vidal M; Goldberg L; Deng H; Hornick MC; Prior J; Worms DP; Long F; Cagan R; Weilbaecher KN
Introduction: Bone is the most common target of metastasis in breast cancer. Osteoclasts (OC) and tumor cells are both known to produce growth factors that support the activity of the other, making the bone microenvironment a hotspot of tumor metastasis. The Hedgehog (Hh) pathway plays a critical role in tumor development and is upregulated in human breast carcinoma cell lines. Copy loss of the pathway inhibitor *Ptch* or gain-of-function mutations of the pathway activator *Smoothened* (SMO) can lead to tumor initiation and progression. Our lab has previously demonstrated that inhibitors of SMO are powerful anti-metastatic compounds. We hypothesize that Hh inhibition exerts anti-tumor effects directly by inhibiting the growth of tumor cells as well as indirectly by altering the bone microenvironment. If our hypothesis is correct, the SMO antagonist LDE225 should effectively stop *in vivo* tumor growth even in MDA-MB-231, a human breast cancer cell line with resistance to Hh inhibition.
Methods: *In vitro* experiments studying effects of LDE225 on proliferation and gene expression of MDA-MB-231 cells and OC's were performed. Balb/c mice injected subcutaneously with MDA-MB-231 tumor cells were treated orally with LDE225 for 21 days, and tumor size was measured regularly.
Results: Viability assays performed on MDA-MB-231 cells treated with LDE225 *in vitro* showed resistance to killing, while qPCR results showed no decrease in expression of Hh target genes *Ptch1* or *Gli2*. However, subcutaneous tumor growth of MDA-MB-231 cells in mice was significantly reduced by LDE225 treatment. Further qPCR analysis of MDA-MB-231 reveals high gene expression of Sonic Hedgehog ligand, suggesting that the tumor cell induces Hh pathway activation in OC's via a possible paracrine mechanism.
Conclusions: These data demonstrate that inhibition of the Hh pathway can reduce breast cancer tumor burden, regardless of tumor Hh responsiveness, through effects on tumor cells and osteoclasts within the tumor microenvironment, making Hh a promising therapeutic target for cancer and bone metastases.

130 **Purusothaman, Vaishnavi**
Medical Student
David F. Silbert Summer Fellowship Award
Summer Research Program
Department of Internal Medicine, Washington University in St. Louis School of Medicine
Mentors: Robyn S. Klein, MD, PhD; Lillian Cruz-Orengo, PhD
CXCL13 neutralization in relapsing and remitting experimental autoimmune encephalitis
Purusothaman V; Cruz-Orengo L; Klein RS
Introduction: Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal loss. Although the pathogenesis of MS is believed to be primarily mediated by autoreactive T cells, more recently a critical role for B cells in the pathogenesis of MS involving the formation of B cell containing ectopic lymph node type structures has been described. CXCL13, a secondary lymphoid chemokine, has been implicated in the formation of these ectopic lymph node type structures. In this study we aim to evaluate the effect of CXCL13 neutralization on the clinical outcomes of mice with relapsing and remitting EAE and whether this clinical effect of CXCL13 is correlated with the presence of ectopic lymph node type structures in the meninges of mice with relapsing and remitting EAE.
Methods: 35 Female SJL mice immunized for active induction of EAE with PLPp139-151 were treated via a retro-orbital injection with polyclonal CXCL13 neutralizing antibody or a control goat IgG either at onset of disease or during first remission. Animals were followed daily and scored on a scale of 1-5. To preserve the meninges so as to better identify ectopic lymph node structures, we performed a decalcification optimization experiment comparing the following four techniques in CNS tissue derived from untreated immunized animals: normal frozen, EDTA-G, 6% TCA, and EDF. Preservation of morphology was evaluated with H&E and preservation of immunogenic epitopes was evaluated based on IHC for CD31, a maker for endothelial cells.
Results: The animals are still currently being followed. 6% TCA solution was identified as the best decalcification solution based on preservation of the meninges and a strong CD31 signal.
Conclusions: An effect of CXCL13 neutralization on the clinical outcome of mice would suggest a possible therapeutic avenue for the treatment of MS. We plan to use the 6% TCA solution to preserve the meninges and look for the presence of ectopic lymph node type structures in the CNS of immunized animals.

Dean's Fellowship

108 **Akhtar, Usman**
Medical Student
Dean's Fellowship
Summer Research Program
Division of Pediatric Neurosurgery
Department of Neurosurgery, Washington University in St. Louis School of Medicine
Mentor: David Limbrick, MD, PhD
Neurosurgical treatment of refractory post-traumatic epilepsy in children
Akhtar U; Limbrick D
Introduction: Traumatic Brain Injury (TBI) is among the leading causes of childhood morbidity and 10-20% of patients with TBI develop Post-traumatic Epilepsy (PTE). Children are particularly susceptible to PTE because the risk of developing PTE increases with younger age. While anticonvulsant medications are frequently effective in controlling seizures in children with PTE, up to one third will be refractory to medical treatment. In these children, epilepsy surgery is often considered. Currently, there are no reliable data for physicians on the types of surgical interventions best suited for PTE. The goal of this study is to overcome the dearth of research in this particular topic with the goal to define the efficacy of epilepsy surgery for PTE and to identify the optimal surgical approaches for common injury patterns.
Methods: In this retrospective clinical report, each patient's pathology is characterized through his or her MRI, EEG and histopathology reports. The MRI and EEG correlated well, and in each case, they pointed to either a focal or diffuse epileptogenic zone. Those with diffuse epilepsy were treated with palliative surgeries, whereas those with focal epilepsy were treated with resections or hemispherotomies. For each of the patients, we examined the overall efficacy of surgical management, and will include final Engel class by injury mechanism, injury pathology, and surgical approach.
Results: This analysis will define the efficacy of surgical interventions for PTE. The initial analysis indicates that the use of hemispherotomy (for focal lesions) is significantly more effective than lobectomy and corpus callosotomy as indicated by comparison of Engel class.
Conclusions: While the individual burden of PTE is overwhelming and the overall impact on healthcare is significant, research is desperately lacking in this area. Currently, there are no reliable data for physicians on the types of surgical interventions best suited for PTE. The goal of this study is to overcome the dearth of research in this particular topic with the goal that the results of this project will serve as a guide for pediatric neurosurgeons as to which procedure to use for a specific kind of PTE.

068 **Bery, Amit**
Medical Student
Dean's Fellowship
Summer Research Program
Division of Plastic and Reconstructive Surgery
Department of Surgery, Washington University in St. Louis School of Medicine
Mentor: Susan Mackinnon, MD
Injury related to extrafascicular and intrafascicular injection of three local anesthetics (1% lidocaine, 0.5% bupivicaine, and 0.5% ropivicaine) into the rat sciatic nerve model
Bery A; Mackinnon S
Introduction: Local anesthetics are used clinically for nerve block. The intraneural placement of these anesthetics has been associated with nerve damage. The purpose of this study is to assess the degree of injury related to extrafascicular and intrafascicular injection of these anesthetics in the rat sciatic nerve model.
Methods: Eighty adult male Lewis rats were divided into ten groups (n=8). Each group was assigned an anesthetic or control for injection (0.9% saline, 10% phenol, 1% lidocaine, 0.5% bupivicaine, or 0.5% ropivicaine) and a location of placement (extrafascicular or intrafascicular). Eight microliters of anesthetic or control were injected into the tibial nerve 5mm distal to the trifurcation of the sciatic nerve. Animals were analyzed for maximum tetanic force of the gastrocnemius muscle and nerves were harvested for histomorphometric analysis by electron microscopy.
Results: Maximum tetanic muscle force for the gastrocnemius muscle was not different between anesthetic groups and saline controls. This result is anticipated in the histomorphometric analysis as well.
Conclusions: These results do not necessarily imply that these anesthetics are safe for intraneural placement. This experiment is being continued with higher injection volumes (50µL) that will allow for a better assessment.

069 **Bokshan, Steven**
Medical Student
Dean's Fellowship
Summer Research Program
Department of Surgery, Washington University in St. Louis School of Medicine
Mentor: William Chapman, MD

Investigation of the utility of three-dimensional intraoperative navigation during hepatic resection: a data registry design

Bokshan SL; Balachandran P; Upadhya GA; Vachharajani N; Anderson CD; Chapman WC

Introduction: In recent years**,** hepatic resection has become a life-saving therapeutic approach in the amelioration of several types of liver cancer. Many hepatic resections, however, are often complicated by the inability to view underlying hepatic structures. The purpose of this study is to examine the legitimacy of current three-dimensional intraoperative navigation technology that allows a surgeon to visualize the underlying structures of the liver in real time during hepatic resection.

Methods: Data from all cases of hepatic resection done by the transplant surgeons of our institution for the next 18 months will be considered for the registry, with a goal of approximately 100 subjects enrolled over the time period. For each resection in which the intraoperative system is used, we will examine several measures of operative success including the volume of blood lost by the patient during surgery, the incidence of biliary leak, and the occurrence of postoperative hepatic insufficiency due to a small remnant of liver (defined as the existence of abnormal prothrombin times or bilirubin levels five days post surgery).

Results: The 3D image-guided system is expected to improve the surgeon's visualization of the surgical field. Therefore, based on our previous experiences with stereotaxis in hepatobiliary surgeries, we expect to observe significant accuracy in volumetrics and execution of resections along preoperatively planned resection planes. This is also expected to decrease postoperative complications including incidence of biliary leak and hepatic insufficiency due to a small liver remnant.

Conclusions: Recently, our 3D intraoperative navigation system (along with similar systems) has prevailed as one of the leading and potentially lifesaving innovations in 3D intraoperative navigation for hepatic resection. However, this product must be empirically and objectively studied prior to full-scale implementation. This study represents one of the first to take such an empirical approach toward 3D intraoperative navigation products.

125 **Chen, Jacqueline**
Medical Student
Dean's Fellowship
Summer Research Program
Department of Neurosurgery, Washington University in St. Louis School of Medicine
Mentor: Neill Wright, MD

Evaluation of dizziness in cervical spine patients

Chen J; Wright N

Introduction: A common complaint of patients presenting with cervical spine problems is dizziness. It is well known that patients presenting with cervical spine problems have an increased overall occurrence of vertigo, but the mechanism and association is not well-understood. The purpose of this study is to evaluate patients seen for cervical spine consultations and to gather and analyze data on the quality of their dizziness as well as their cervical spine outcomes.

Methods: The study performed was a retrospective data analysis of 344 patients seen by Dr. Neill Wright for cervical spine consultation. Using AllScripts, patients were evaluated based on 24 data points collected about their medical history, past medical history, physical exam, radiology, and assessment. Patients with a history of head trauma or ear surgery were excluded, as well as patients whose dizziness charts were missing or incomplete.

Results: We anticipate that the results of this study will shed some light on which cervical spine diseases are likely correlated with increased presentation of dizziness. Furthermore, we hope that the results will increase our understanding of the disease mechanisms behind the symptoms. This study is only the first step to achieving that understanding, but as this is a poorly understood subject, it will provide the basis for future understanding.

Conclusions: Many patients suffering from cervical spine problems also experience dizziness. It is to the benefit of both patients and physicians to understand the correlations and mechanisms behind this presentation. The importance of this study lies in the improvement of patient diagnosis, management, and outcomes.

035 **Donaldson, Sarah EJ**
Medical Student
Dean's Fellowship
Summer Research Program
Hematology Branch, NHLBI
Department of Occupational Therapy, Washington University in St. Louis School of Medicine
Mentors: Neal S. Young, MD; Allison King, MD
Serum sickness in the treatment of severe aplastic anemia with horse or rabbit antithymocyte globulin
Donaldson SEJ; Feng X; King A; Young NS
Introduction: Severe aplastic anemia (SAA) is treated by immunosuppression with antithymocyte globulin (ATG) plus cyclosporine in patients without matched bone marrow donors. Horse and rabbit ATG were compared by a recent randomized control trial, which showed that horse ATG was markedly superior as measured by hematologic response after three months. In addition, fewer hATG-treat patients suffered from serum sickness (SS), a common complication of ATG treatment. The objective of this study was to compare ATG concentrations and anti-ATG antibody in SAA patients without SS.
Methods: Enzyme-linked immunosorbent assay was performed to find hATG/rATG concentrations and human anti-ATG antibody titers in plasma of SAA patients treated with hATG or rATG.
Results: Concentration of ATG decreased gradually soon after treatment, with a more rapid decrease seen for SS patients. Significant differences between concentrations of rATG were found between SS and non-SS patients at the two and three week timepoints P=0.0013, P=0.0003 but for hATG the groups did not differ significantly at the combined two and three week timepoints P=0.1686. Human IgM, IgG, and IgA against rATG in SS patients were significantly higher than those of non-SS patients, and IgM against hATG was significantly greater for SS patients between 12 and 21 days after treatment
Conclusions: The trend towards higher incidence of serum sickness in rATG-treated patients and the significantly higher IgG, IgA, and IgM against rATG in their plasma after treatment suggests that rATG is less safe as a treatment for SAA. This, in addition to the superiority of the therapeutic effect of hATG demonstrated by the clinical trial, indicates hATG as the clear choice for a first line treatment in SAA.

093 **Dornfeld, Jarrod**
Medical Student
Dean's Fellowship
Summer Research Program
Department of Infection & Immunology, University of East Anglia, Great Britain
Department of Pathology & Immunology, Washington University in Saint Louis School of Medicine
Mentors: Tom Wileman, PhD; Barry Sleckman, MD, PhD
Murine gut organoid culture and examination of autophagy in mouse fibroblasts
Dornfeld JA; Wileman T
Introduction: Examining autophagy responses in the gut have proven difficult in the past due to difficulty in creating *in vivo* behavior of intestinal crypts in a laboratory setting. The purpose of this project was to help develop a protocol for converting *in vivo* gut crypts into *in vitro* organoids that can be used for testing innate immunity. This project also used immunohistochemistry to test a transgenic mouse carrying a GFP-tagged LC3 gene, a major protein in the autophagy process.
Methods: A barebones protocol for crypt isolation was used and adjusted in various ways to improve the protocol's efficiency. Mouse fibroblasts from a GFP-LC3 mouse were isolated using skin cells and examined under fluorescent microscopy.
Results: A protocol was developed that elicited almost 10% initial survival rate of crypts, which was considerably more than the previous procedure. Splitting the cultured organoids often resulted in minor loss, but it was not significant. Fluorescent microscopy of the mouse fibroblasts when examined under starvation conditions and application of Poly I:C resulted in striking images illustrating a robust autophagic response.
Conclusions: The development of a consistently working protocol for organoid isolation will hopefully lead more researchers to investigate the field. It still needs work, but the method is certainly more fine-tuned now. In addition, it is clear that the GFP-LC3 mouse functions very well. The immunohistochemistry success paired with a viable isolation method may lead to novel methods of examining immune responses in the gut. Such methods may include treatments that only contact the apical sides of crypts, which have proven very difficult with current practices.

083 **Dvoracek, Lucas**
Medical Student
Dean's Fellowship
Summer Research Program
Department of Otolaryngology, Washington University in St. Louis School of Medicine
Central Institute of the Deaf, Washington University in St. Louis
Mentor: Jianxin Bao, PhD

A method for analyzing the spatial distribution of ribbon synapses in cochlear hair cells

Dvoracek LA; Bao J

Introduction: Presbycusis (or age-related hearing loss) is reaching epidemic status in America. The development of pharmaceutical methods for abrogating presbycusis depends on a thorough understanding of the way in which these treatments affect the progression of cochlear hair cell/nerve synaptic degradation. Current methods for evaluating the spatial distribution of these synapses are exceedingly subjective. The aim of this study is to generate an objective approach for assessment of these synapses, both in their native arrangement and drug-modified arrangements.

Methods: Mouse cochleae were immunostained for pre-synaptic ribbon synapses, post-synaptic AMPA receptors, nuclei, and hair cell cytoplasm. High-resolution images acquired from confocal microscopy of these cochleae were analyzed via software and custom MATLAB routines to generate a spatial distribution map of the synaptic structures.

Results: A novel method for objective characterization of synaptic distribution in hair cells was developed. This four-dye staining of cochleae protocol and the software-based analysis methods developed will enable accurate depiction of hair cell synaptic relationships. Further improvements will be made as coordinate normalization protocols are modified to increase consistency among hair cell orientations.

Conclusions: This method will enable a grasp of the effects of pharmaceutical treatments on presbycusis in an accelerated age-related hearing loss mouse model to be evaluated objectively and consistently. These data will be crucial in establishing the case for revised clinical indications for use of these drugs in preventing the onset of presbycusis. Upon thorough appraisal of the proper dosing of effective drugs and confirmation that these substances do not exhibit problematic side effects at these dosages in mice, clinical trials of these drugs may be performed. Ultimately, this may generate a pharmaceutical intervention for presbycusis progression which will maintain one aspect of quality of life for millions of individuals at risk for age-related hearing loss.

016, 017, 018 **Ebersole, Gregory C**
Medical Student
Dean's Fellowship
Summer Research Program
Department of Surgery, Washington University in St. Louis School of Medicine
Mentor: Corey R. Deeken, PhD

Development of novel electrospun absorbable polycaprolactone (PCL) scaffolds for hernia repair applications

Ebersole GC[*]; Buettmann EG[*]; MacEwan MR, Tang ME; Frisella MM; Matthews BD; Deeken CR
[*]*These authors contributed equally to this work.*

Introduction: Electrospun scaffolds are a novel class of biomaterials which may provide a unique platform for the design of increasingly advanced soft tissue repair materials. Unlike currently available hernia repair materials, absorbable electrospun scaffolds possess the ability to direct cellular orientation through the presentation of ordered topographical cues and to prevent fibrosis through resorption of the scaffold. The purpose of this study was to develop a variety of electrospun meshes and to evaluate the morphological characteristics of these materials to determine their suitability for hernia repair applications.

Methods: High molecular weight (MW) and low MW polycaprolactone (PCL) were solubilized at a variety of concentrations in a 4:1 mixture of dichloromethane and N,N-dimethylformamide. These solutions were then electrospun. Flow rate, applied voltage, and needle tip to collector plate distance were altered to produce consistent scaffolds. Scanning electron microscopy was performed to evaluate scaffold microstructure.

Results: The high MW PCL solutions produced more consistent microstructures than the low MW solutions. Higher wt/vol% solution reduced the appearance of beading. Changes in flow rate did not significantly alter fiber diameters.

Conclusions: Electrospinning was utilized to develop fibrous PCL scaffolds of a consistent microstructure. Future studies will focus on parameters such as alteration of fiber diameter, cross-linking procedures, and scaffold chemistry and the influence over mechanical strength.

098 **Feng, Daniel**

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Mentor: Christopher Carpenter, MD, MSc

Validity of the triage risk screening tool (TRST) and identification of seniors at risk (ISAR) instrument as predictors for mortality, ED revisit, hospital readmission, nursing home admission, and functional decline in geriatric ED patients

Feng D; Li S; Abboud S; Carpenter CR

Introduction: ED revisit, post-ED hospitalization, nursing home (NH) admission, and functional decline are key challenges for improving geriatric medical care and quality of life. The Triage Risk Screening Tool (TRST) and Identification of Seniors at Risk (ISAR) were developed to predict suboptimal post-ED geriatric outcomes. These instruments have only been validated in the regions where they were derived, and further research is needed to confirm their ED applicability. In addition, TRST and ISAR have never been validated for cognitively impaired individuals, who comprise a majority of geriatric ED visits.

Methods: This was a prospective, observational cohort study of all consenting ED patients age 65 and older in a private, urban, academic hospital between June 1 and July 31, 2011. Within a larger RCT, trained geriatric technicians administered the Older American Resources and Services Activities of Daily Living (OARS-ADL) scale, Short Blessed Test (SBT) for dementia, TRST, ISAR, and several other screenings. At 30 days post ED, mortality, ED revisit, hospitalization, NH admission, functional decline (a ≥3-point decline on OARS-ADL), and the composite outcome were measured via telephone follow-up. Participants were excluded at follow-up if they had received a cognitive intervention used in the larger RCT. ROC curves with area under the curve (AUC) and likelihood ratios were calculated for the predictive validity of TRST and ISAR in individuals with no evidence (SBT score≤4) and evidence (SBT>4) of cognitive impairment.

Results: Participants (N=168) had a mean age of 74, were 43.1% male, and 62% African-American. TRST and ISAR stratified 81% and 79% at high risk for composite outcome (score>2). ISAR and TRST had AUCs of 0.70 and 0.64 for composite outcome at 30 days, exhibiting moderate and poor validity, respectively. ISAR had moderate predictive validity for composite outcome in patients with no cognitive impairment (-LR = 0.20, N=25).

Conclusions: ISAR may have some validity for suboptimal outcomes in geriatric ED patients with no cognitive impairment.

081 **Fritz, Bradley A**

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Recovery in the post-anesthesia care unit (PACU) in the BAG-RECALL and B-Unaware randomized control trials

Fritz BA; Rao P; Avidan MS

Introduction: Use of the bispectral index (BIS) processed electroencephalogram may decrease excessive anesthetic drug administration, leading to reduced incidence of delayed or complicated recovery from general anesthesia. Examples of complicated recovery include postoperative nausea and vomiting, as well as severe postoperative pain. The purpose of this study is to describe the effect of using a BIS-based anesthetic protocol on several recovery-related outcomes.

Methods: 6,700 patients at high risk for intraoperative awareness were randomized to receive general anesthesia following either a BIS-guided protocol or an end tidal anesthetic concentration (ETAC)-guided protocol. Differences in outcomes between the two groups were assessed using univariate Cox regression or chi square tests.

Results: The BIS and ETAC cohorts did not differ in incidence of postoperative nausea and vomiting (OR = 1.0, 95% CI 0.7-1.5), incidence of severe postoperative pain (OR = 0.8, 95% CI 0.6-1.1), time to achieve an Aldrete score of 9-10 (HR = 1.2, 95% CI 1.0-1.4), PACU length of stay (HR = 1.0, 95% CI 1.0-1.1), or ICU length of stay (HR = 1.0, 95% CI 0.9-1.1).

Conclusions: Following a BIS-guided protocol rather than an ETAC-guided protocol does not appear to change the time needed for recovery, the incidence of postoperative nausea and vomiting, or the incidence of severe postoperative pain following general anesthesia in patients at high risk for intraoperative awareness.

101 **Gammon, Harrison**
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Mentor: Anjali Bhorade, MD
On-road driving performance of visually impaired glaucoma patients
Harrison G; Bhorade A
Introduction: In North America, glaucoma is a leading cause of irreversible yet preventable visual field loss. This disease is a major public health issue not only for its gradual yet deleterious effects on peripheral vision, but also because the affected population, often under-diagnosed, continue to drive motor vehicles. No study to date has specifically compared driving abilities of non-glaucomatous patients with moderate to severe glaucoma patients in true vehicle, open-road settings. The purpose of this study is to demonstrate the relationship between moderate to severe glaucoma and driving compared to age, gender-, and race-matched controls, and to measure the extent of driving performance deficit in a setting that most closely resembles normal driving conditions.
Methods: This is a prospective case-control cohort study. Patients with glaucoma will be recruited from the Glaucoma Clinic at Washington University. Consecutive qualifying patients will be asked to participate in the study until the goal of 30 consented patients who have undergone the on-road driving test has been met. The control cohort will be recruited in collaboration with Dr. Carr's research group, which has had extensive previous experience in conducting driving studies among the elderly and neurologically impaired.
Results: It is anticipated that glaucomatous individuals with classification of moderate to severe disease will show poor performance on the on-road driving test compared to a group of matched controls. Early data supports this conclusion, but it is unclear yet whether data will be statistically significant.
Conclusions: Glaucoma is a common ophthalmic disease that may have a significant impact on driving. It is important that the risk of driving with moderate to severe glaucoma is understood so that patients with these diagnoses can be appropriately counseled on the dangers to themselves and others caused by their driving. It is hoped that study results will lead to the development of a screening tool to determine driving eligibility for individuals with glaucoma.

082 **Gershuni, Victoria, MS**
Medical Student
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Mentor: L. Michael Brunt, MD
Improving senior medical student suturing and knot tying skills through proficiency-based training
Gershuni VG; Bittner JG; Brunt LM
Introduction: The purpose of this prospective study was to evaluate outcomes of a proficiency-based suturing and knot-tying skills curriculum for medical students pursuing a surgical career.
Methods: A basic suturing and knot-tying curriculum was designed by one senior surgeon (LMB). Voluntary participants included senior medical students (n=11) pursing a surgical residency. Following enrollment, subjects underwent initial proficiency testing and then 45 minutes of didactic instruction and 2 hours of hands-on practice of suturing and knot tying (simple interrupted, running subcuticular, one- and two-handed tie, and tie on pass). Subjects were given materials and proficiency targets for practice, and 3 weeks later returned for a 1-hour proctored session. After 2 months of surgical rotations, subjects completed final proficiency testing. Objective Structured Assessment of Technical Skills (OSATS, 1=novice, 3=proficient, 5=expert) and cumulative task time were used to evaluate pre- and post-course technical skills. Subjects were compared to a control group of PGY1 surgical interns (n=8) who completed a similar curriculum and to end of R2 (n=6) surgical residents. Statistical analysis was done using non-parametric tests. Data are presented as mean and standard deviation.
Results: Following completion of the curriculum, medical student OSATS scores (2.0$\pm$.2 vs 3.1$\pm$.3, p<.01) and total task time (855.4$\pm$190.4 vs 538.8$\pm$92.5 sec, p< .01) improved significantly. PGY1 OSATS scores (2.1$\pm$.6 vs 2.7$\pm$.7, p=.08) were unchanged but task time decreased (773.4$\pm$169.7 vs 601.3$\pm$74.4sec, p=.02). After completion, medical students reached proficiency with a lower OSATS score compared to R2 surgical residents (3.1$\pm$.3 vs 3.6$\pm$.3, p<.01) but with similar total task times (538.8$\pm$92.5 vs 474.8$\pm$81.2 sec, p=.20).
Conclusions: A curriculum-driven, proficiency-based surgical skills course for senior medical students is feasible and can result in technical proficiency for basic suturing and knot tying tasks at a level comparable to R2 residents. Offering this program early in the senior year may confer advantages over typical "boot camp" courses given late in the 4th-year or at the beginning of internship.

110 **Harris, David C**

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Mentor: Rick W. Wright, MD

Radiographic analysis of revision ACL reconstruction

Harris DC; Tarabichi M; Haas A; Wright RW

Introduction: Anterior cruciate ligament (ACL) injury can significantly impact knee stability and function in the short term and lead to osteoarthritis in the long term, so most patients elect to have reconstructive surgery to mitigate these effects. However, revision ACL reconstructions after additional ligament failures have been associated with higher rates of recurrence and worse patient outcomes as compared to primary ACL reconstructions. Technical errors occurring during surgery are believed to be the primary cause of repetitive ACL insufficiency requiring surgical revision. Ordinary x-rays are a simple and low-cost means of identifying tunnel locations and joint pathologies that can complicate reconstructions and result in poor outcomes.

Methods: Plain preoperative radiographs from the Multi-center ACL Revision Study (MARS) patient cohort were analyzed for tunnel placement, joint space narrowing, and knee malalignment on a variety of views, including lateral full extension, standing AP, Rosenberg 45° bent-knee weightbearing, and hip-knee-ankle alignment films. Separately, these data will be correlated with radiological osteoarthritis classification grade and two year patient outcome to determine the predictive value of preoperative radiologic measures on long-term results.

Results: Technical issues that merit special surgical consideration, such as tunnel malposition, will be visible on preoperative review of patients' plain knee radiographs. Additionally, patients who exhibit knee pathologies including excessive varus or valgus malalignment or significant joint space narrowing will experience worse clinical outcomes.

Conclusions: Femoral and tibial tunnel placement, joint space narrowing, and varus or valgus malalignment will all be identifiable on plain radiographs, and preoperative assessment of these factors will guide future efforts to reduce failure rate and improve long-term patient outcomes.

102 **He, Yizheng**

Medical Student
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Mentors: David Van Essen, PhD; Matthew Glasser

Construction and registration of post-mortem macaque brain's white-matter surface

He Y; Glasser M; Van Essen D

Introduction: The white matter tracts within the primate brain are incompletely mapped. Here we construct the white-matter surface of a post-mortem macaque brain in order to work towards the goal of elucidating the connections between different regions of the primate brain.

Methods: Individual voxels of the entire volume of the diffusion data had to be manually edited using the anatomical image as a guide in order to correctly infer the contours of the surface. Caret 5 software was used to perform the manual voxel-wise editing of the surface. First, the diffusion dataset was thresholded to a value that approximated the white-matter surface structure. This image was then binarized into the starting image. From this, the cerebellum was completely erased from the image by making a cut through an oblique plane. Next, the image was divided into the left and right hemispheres. Then voxels were either added or deleted from the image in order to 1) follow the general contours of the white-matter surface using the anatomical image as a guide and 2) minimize topological errors (avoiding handles in the surface). A surface was generated for each hemisphere and finally, the surface was registered onto a standard macaque atlas by manually drawing 31 landmarks and using Caret software to deform the surface accordingly.

Results: Inspection of the registration revealed some mismatches, so four extra landmarks were added and the surface was re-registered to fix this problem. The registration showed good correspondence between landmarks on the white-matter surface and the standard macaque atlas.

Conclusions: This is part of a larger effort to map the human "connectome", a comprehensive map of neural connections in the brain. Having the white-matter surface allows us to perform tractography analysis on the brain in order to generate a map of the white-matter connections within the macaque brain. Eventually, a comprehensive understanding of the anatomical connections in the brain will pave the way for better therapeutic interventions in diseases caused by abnormalities in the connectome.

111 **Hoerter, Nicholas**

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Mentors: Joel Perlmutter, MD; Meghan Campbell, PhD; Samer Tabbal, MD

Correspondence of microelectrode recordings and fiducial-based atlas registration for localization of deep brain stimulation contacts in the subthalamic nucleus

Hoerter N; Perlmutter J; Campbell M; Tabbal S; Karimi M; Lugar H

Introduction: The location of deep brain stimulation (DBS) electrode contacts within the subthalamic nucleus (STN) may account for variable behavioral, cognitive, and motor responses in Parkinson's disease patients. Various methods are used to locate DBS contacts, but they are rarely compared. The first aim of the study is to assess the correspondence between two methods, post-surgical atlas registration and microelectrode recordings (MER). The second aim is to determine whether electrode position relative to the STN is related to clinical outcome using the Universal Parkinson Disease Rating Scale (UPDRS).

Methods: The two methods were compared for 85 subjects by measurement of the STN span along the electrode trajectory and distance from the target (0 for MER) as determined by each method. UPDRS improvement 3-12 months after surgery was compared between subjects with electrodes inside the STN and subjects with electrodes outside the STN, determined by atlas registration.

Results: The two methods showed significantly different STN spans in a paired t-test ($t(123) = -11.86$, $p < .001$), and distance from the target as measured by the atlas registration technique was significantly different from zero using a single sample t-test ($t(123) = 15.559$, $p < .001$). However, there was a positive, statistically significant correlation between the STN spans, shown by a Pearson correlation ($r = .261$, $N = 124$, $p = .003$). UPDRS improvement in subjects with electrodes inside or outside the STN were not significantly different in a Mann-Whitney U test ($U = 597$, $p = .251$).

Conclusions: The difference between the two methods in combination with the significant correlation suggests that a systematic bias may exist in one method, but the localization methods are related. The similarities in UPDRS improvement between different electrode positions indicate that the therapeutic target for DBS is large. To evaluate these questions further, the method used for extracting contact locations from MER could be improved.

071 **Jacobsen, Kyle**

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Hiatal hernia repair with or without esophageal lengthening: Is there a difference?

Puri V; Jacobsen K; Bell J; Crabtree TD; Kreisel D; Krupnick AS; Patterson GA; Meyers BF

Introduction: The need for esophageal lengthening (EL) as part of hiatal hernia repair is thought to elevate perioperative risk and provide functionally inferior outcomes. We hypothesized that operative and functional outcomes for hiatal hernia repair were similar in patients whether they required EL or not.

Methods: Review of institutional experience with EL as part of hiatal hernia repair. Patients underwent before and after symptom evaluation using a validated tool.

Results: Between 1999 and 2009, 375 patients underwent hiatal hernia repair. The operative approach was: Thoracotomy 153 (41%), Laparotomy 23 (6.1%), Laparoscopy 167 (46%) or combined 32 (8.5%). All patients underwent a fundoplication. Of these, 167 (45%) required EL. There was a higher need for thoracotomy in patients undergoing EL (79/167 vs 74/208, X^2=5.27p=0.026). The incidence of perioperative complications (leak, pneumonia, ileus, respiratory failure, bleeding) was similar between the two groups. 65 patients undergoing EL were compared to 63 patients with comparable demographics not requiring EL. In a well-validated before and after questionnaire, patients undergoing EL showed significant improvement in their heartburn (76.8%), dysphagia (67.6%), regurgitation (71.7%), chest pain (91.9%) and nausea (86.5%) ($p<0.05$). The patients not undergoing EL also showed significant improvement in their heartburn (81.1%), dysphagia (71.1%), regurgitation (64.4%), chest pain (64.1%) and nausea (61.0%) ($p<0.05$). Improvement in symptoms, the continued use of antacid medications and overall surgery satisfaction score were statistically similar between the two groups.

Conclusions: Operative and functional outcomes for hiatal hernia repair with or without EL are acceptable and comparable. Thoracic surgeons should utilize EL without reservations for appropriate indications.

104 **Kim, Jenna M**
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Mentor: Anjali Bhorade MD

On-road driving performance of visually impaired glaucoma patients compared to normal control participants

Yom V; Kim JM; Gammon H; Kambarian J; Bhorade A

Introduction: Glaucoma is a major public health issue not only for its gradual yet deleterious effects on peripheral vision, but also because the affected population, often under-diagnosed, continue to drive motor vehicles. Few studies have been published to date concerning the effects of eye diseases on driving and no study to date has specifically compared driving abilities of non-glaucomatous patients with moderate to severe glaucoma patients in true vehicle, open-road settings. The purpose of this study is to demonstrate the relationship between moderate to severe glaucoma and driving compared to age, gender-, and race-matched controls, and to measure the extent of driving performance deficit in a setting that most closely resembles normal driving conditions.

Methods: Visual patients with glaucoma stage of 2 or greater (moderate to severe) in both eyes were selected from Center for Advanced Medicine in Washington University in St. Louis and evaluated for their driving on-road on dual-brake car with a driving instructor. So far 19 glaucoma patients and 41 age- and gender-matched control participants have completed the driving study.

Results: Overall, drivers with moderate to severe glaucoma are twice as likely (16% versus 7%) to fail the on-road driving test compared to normal control drivers. Glaucoma patients also required more interventions with braking and steering wheel, three time four times as much as healthy controls, respectively. There is negligible difference in education level or cognitive abilities between the two groups.

Conclusions: While the results are preliminary due to the small number of glaucoma patients who have completed the study, the results of this study already suggest that the effect of glaucoma on visual input is significant and thus has negatively impacts driving abilities. The study should continue to enroll more eligible glaucoma patients in the study to validate the preliminary results. Results from the full study may be used to promote change in the current requirements for drivers' licensing and limit driving by those with severe glaucomatous visual loss for public safety.

105 **Klemisch, Rob**
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Comparing emergency medicine practices for central venous catheter placement to existing ICU checklists

Klemisch R; Theodoro D

Introduction: The incidence of Central Venous Catheter (CVC) insertion is increasing in the Emergency Department (ED). Checklists for CVC placement have been shown to increase adherence to best practices and reduce central line associated blood stream infections. Though multiple checklists have been published for use in the Intensive Care Unit (ICU), none has been tailored to the ED. The objective was to perform a pilot study to assess ED utilization of well accepted CVC checklists and determine adherence to specific checklist elements related to infection control.

Methods: This was a convenience sample of CVC insertions in an urban Level I trauma ED performed between June and August 2011. CVC insertions by ED physicians were captured by an independent, trained observer on staggered shifts including days, evenings, and overnights. "Crash" CVC insertions (defined as placed under imminent life or death conditions) were excluded. Observed ED CVC placements were compared to elements of four non-ED checklists. We used descriptive statistics to identify areas of high and low adherence.

Results: The CVC "bundle" was used by 19 of 19 operators (100%, 95%CI 0.83 to 1) and in 19 of 19 (100%, 95%CI 0.83 to 1) cases the included checklist was discarded. No operator completed all elements on any of the four checklists. Sterile gloves were used in 19 of 19 insertions (100%, 95%CI 0.83 to 1), sedation or local anesthetic was used in 18 of 18 (100%, 95%CI 0.83 to 1), and maintenance of a sterile field throughout the procedure was observed in 17 of 17 (100%, 95%CI 0.82 to 1). Operators wore caps and masks during 16 of 19 insertions (84%, 95%CI 0.62 to 0.94) and gowns during 18 of 19 insertions (95%, 95%CI 0.75 to 0.99). In 9 of 19 insertions (47%, 95%CI 0.27 to 0.68) patients were not draped from head to toe, 8 of 18 insertion sites (44% 95%CI 0.25 to 0.66) were not scrubbed for a full 30 seconds, 7 of 17 (41% 95%CI 0.21 to 0.64) operators did not clamp all unused lumens, and in 9 of 16 insertions Trendelenburg position was not used (56%, 95%CI 0.33 to 0.77).

Conclusions: This small pilot study demonstrated that ED physicians have not adopted CVC checklists. In addition, adherence to these established checklist practices are poor. Outcomes of ED central lines may benefit from an ED developed, structured checklist.

098 **Li, Sophia**

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Validity of the triage risk screening tool (TRST) and identification of seniors at risk (ISAR) instrument as predictors for mortality, ED revisit, hospital readmission, nursing home admission, and functional decline in geriatric ED patients

Li S; Feng D; Abboud S; Carpenter CR

Introduction: ED revisit, post-ED hospitalization, nursing home (NH) admission, and functional decline are key challenges for improving geriatric medical care and quality of life. The Triage Risk Screening Tool (TRST) and Identification of Seniors at Risk (ISAR) were developed to predict suboptimal post-ED geriatric outcomes. These instruments have only been validated in the regions where they were derived, and further research is needed to confirm their ED applicability. In addition, TRST and ISAR have never been validated for cognitively impaired individuals, who comprise a majority of geriatric ED visits.

Methods: This was a prospective, observational cohort study of all consenting ED patients age 65 and older in a private, urban, academic hospital between June 1 and July 31, 2011. Within a larger RCT, trained geriatric technicians administered the Older American Resources and Services Activities of Daily Living (OARS-ADL) scale, Short Blessed Test (SBT) for dementia, TRST, ISAR, and several other screenings. At 30 days post ED, mortality, ED revisit, hospitalization, NH admission, functional decline (a ≥3-point decline on OARS-ADL), and the composite outcome were measured via telephone follow-up. Participants were excluded at follow-up if they had received a cognitive intervention used in the larger RCT. ROC curves with area under the curve (AUC) and likelihood ratios were calculated for the predictive validity of TRST and ISAR in individuals with no evidence (SBT score≤4) and evidence (SBT>4) of cognitive impairment.

Results: Participants (N=168) had a mean age of 74, were 43.1% male, and 62% African-American. TRST and ISAR stratified 81% and 79% at high risk for composite outcome (score>2). ISAR and TRST had AUCs of 0.70 and 0.64 for composite outcome at 30 days, exhibiting moderate and poor validity, respectively. ISAR had moderate predictive validity for composite outcome in patients with no cognitive impairment (-LR = 0.20, N=25).

Conclusions: ISAR may have some validity for suboptimal outcomes in geriatric ED patients with no cognitive impairment.

040 **McNair, Paul**

Medical Student
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Mentor: Michael Avidan, MD

Anesthetic management of patients with natural red hair

McNair PS; Gradwohl SC

Introduction: There is an anecdotal impression among healthcare practitioners that people with natural red hair require an increase in anesthesia. To determine if red hair plays a role in a patient's response to anesthesia this study seeks to investigate anesthetic management, relationship between depth of anesthesia and anesthetic gas concentration, and incidence of intra-operative awareness between people with red hair and those without.

Methods: This is a pre-specified sub-study of the BAG-RECALL study, a 6,000 patient prospective, randomized trial comparing the use of a processed EEG, BIS, based anesthetic protocol versus an end tidal anesthetic gas, ETAC, based protocol to reduce the incidence of intra-operative awareness. Patients were asked post-operatively if they have natural red hair. The two independent sample t tests, Mann Whitney U, Chi squared, and Fisher Exact tests were used for comparison as appropriate. A linear mixed effects model will be used to assess the relationship between ETAC and BIS for red heads compared to non red heads.

Results: All dosage summations within each class of anesthetic drug, expressed in drug equivalents, and age adjusted MAC values for all volatile gases did not differ significantly between red heads and non red heads, with medians of total age adjusted MAC having a median of 0.915 for red heads and 0.907 for non red heads (p = 0.98). The incidence of intra-operative awareness for red heads, 0.6%, and non read heads, 0.5%, did not significantly differ (p = 0.67). A linear mixed effects model comparing BIS versus ETAC for red heads and for non red heads will be computed.

Conclusions: Neither the anesthetic care nor the incidence of intra-operative awareness of patients with red hair differed significantly from that of non red heads. The linear mixed effects model will shed light onto whether the relationship between depth of anesthesia and anesthetic gas concentration differs between the two groups, which can help to assess whether there is a different physiological response to anesthesia between the two groups. Thus it can be determined if natural red hair should be a factor to consider for anesthetic management of patients.

041 **Morris, Hallie**
Medical Student
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Summer Research Program
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Mentors: Kevin Baszis, MD; Andrew White, MD
Drug regimen and outcomes in juvenile dermatomyositis
Morris H; Baszis K; White A; French A
Introduction: Juvenile dermatomyositis is a childhood autoimmune disease distinguished by symmetrical proximal muscle weakness, raised serum concentrations of muscle enzymes, and characteristic skin rashes. Before the introduction of corticosteroids, a third of affected children died, a third had disabling symptoms (including contractures, calcinosis, and weakness), and most had chronically active disease well into adulthood. Yet recent studies have indicated that an aggressive, multidrug treatment regimen can induce remission in a majority of JDM patients, despite the fact that disease control has been the long-held aim for the majority of rheumatologic diseases. This research aimed to assess the time needed to achieve a sustained medication-free remission in a cohort of patients with JDM based on the drug regimen received.
Methods: Between April 1997 and June 2011, a cohort of 46 children with JDM was followed at St. Louis Children's Hospital, a single tertiary care center. Patients were classified into mild, moderate, and severe categories based on their presenting symptoms. The most common therapy options included steroids, methotrexate, IVIG, rituximab, leflunomide and plaquenil, but other drugs were prescribed as well. The primary outcome measure was time to complete remission. Additional outcome measures were onset of calcinosis and complications resulting from medications.
Results: In 2009, Boston Children's Hospital published a paper supporting an aggressive drug regimen for JDM patients. A complete, medication-free remission was achieved in 28 of 49 patients, with the median time to remission 38 months, and no disease flares during the subsequent period of observation. We are hoping to see equally encouraging numbers using slightly less aggressive treatment regimens. Patients at SLCH also received a more diverse mix of drugs, and we anticipate data on an array of immunosuppressants in treating JDM.
Conclusions: JDM is a complicated disease that varies in its presentation patient by patient. Exactly which drugs work best, or what optimal dosing is, is not widely agreed upon. The more data that can be collected on what works in a cohort and what doesn't, the better treatment regimens will be able to induce remission and limit side effects for young patients with the disease.

095 **Nojan, Miriam**
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Mentors: Reza Jarrahy; Gregory Polites, MD
Negative pressure wound therapy in the management of open tibia fractures necessitating flap reconstruction
Nojan M; Jarrahy R
Introduction: Free flap coverage in the setting of open tibial fractures has been associated with differential complication rates in groups treated acutely versus those managed subacutely, and chronically. Post-operative outcomes of acutely treated patients are associated with lower complication rates. Negative pressure wound therapy (NPWT) was reviewed in this series within the 3 groups to evaluate its effect on outcomes and complications.
Methods: Forty nine patients with open Gustilo Grade IIIB or IIIC tibial fractures who underwent flap reconstruction between 1996 and 2001 were reviewed. Patients were distributed into three groups according to the time-course of their management: acute (flap reconstruction 1 to 7 days after injury), subactute (8 to 42 days after injury), and chronic (>42 days after injury). Outcomes measured were overall complications, infectious complications, flap-revisions, number of surgical procedures, and duration of hospital stay.
Results: Chronically treated groups demonstrated the greatest rate of complications (85.71%) in comparison to subacute (68.18%) and acute (46.15%) treatment groups. Infectious complications were greatest in the subacute group (40.91%) followed by chronic (35.71%) and acute (30.77%). Similarly flap failure was greatest in the subacute group (13.63%) followed by 20% in the chronic treatment group and 0% in those treated acutely. Within the subgroup of patients that received NPWT in each group (acute, subacute, and chronic) there were observed trends towards lower complications in post-operative outcomes.
Conclusions: The results of this study suggest that NPWT as part of a wound care regimen is a useful adjunct in the management of open tibial fractures.

026 **Perlin, Lauren**

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Mentors: Karen Mestan, MD; Jennifer Cole, MD

Determinants of early childhood obesity/overweight in preterm infants with bronchopulmonary dysplasia

Perlin L; Mestan K

Introduction: Little is known about growth, specifically early childhood obesity, in premature babies who develop bronchopulmonary dysplasia (BPD), perhaps because preterm infants are generally considered to achieve poor growth status and are at risk for failure to thrive. However, early feeding practices for these infants may actually lead to increased weight gain, potentially resulting in childhood obesity, a problem that is reaching epidemic proportions in the United States.

Methods: Retrospective chart review of all infants born at less than 33 weeks gestation and admitted to Children's Memorial Hospital between 2005 and 2009. Height and weight up to 5 years of age were recorded. Co-morbidities such as NEC, PDA, IVH, PVL, and ROP were noted.

Results: Of the 453 patients identified, 189 (42%) developed bronchopulmonary dysplasia, defined as requiring supplemental oxygen at 36 weeks gestational age. Infants with BPD were 3.9 times as likely as their healthy counterparts to have at least one weight measurement greater than the 95th percentile (weight measurements ranged from age 6 months to 5 years, when available).

Conclusions: The study results suggest that premature infants who develop bronchopulmonary dysplasia are at risk for being overweight or obese in early childhood. This contradicts many earlier studies that show decreased childhood growth in babies with BPD. Further research is necessary to determine if increased weight gain is directly affected by newer feeding practices for babies with BPD.

016, 017 **Pui, Chi Lun**

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Effect of repetitive loading on the mechanical properties of biologic scaffold materials

Pui CL[*]; Tang ME[*]; Annor AH; Ebersole GC; Frisella MM; Matthews BD; Deeken CR

[*]*These authors contributed equally to this work.*

Introduction: In order to minimize the risk of hernia recurrence or bulging, the scaffolds used in ventral hernia repair must retain their mechanical integrity after repeated cycles of mechanical loading. Such cycles may be generated during daily activities such as jumping, coughing, bending, lifting, and walking up stairs. In this study, nine biological scaffolds were subjected to mechanical strength testing after exposure to repetitive loading sequences.

Methods: The scaffolds were cut into 1x6cm specimens, hydrated, and exposed to 0, 10,100, or 1000 cycles of repetitive loading. A cycle was comprised of loading the specimen up to 16N/cm, followed by unloading back to 0.1N. Information such as load and extension were recorded, and stress, strain, modulus, and plastic deformation were calculated.

Results: Tensile strength remained unchanged for CollaMend, XenMatrix, Veritas, and Surgisis over 0, 10, 100, and 1000 cycles ($p>0.05$). However, Strattice and AlloMax exhibited reduced tensile strength, while Permacol, FlexHD, and PeriGuard exhibited a slight increase in tensile strength with increasing number of cycles. Differences were also observed between crosslinked and non-crosslinked scaffolds of the same tissue type. For instance, crosslinked bovine pericardium (PeriGuard) displayed greater tensile strength than non-crosslinked Veritas throughout all levels of repetitive loading ($p<0.0001$). Similarly, crosslinked porcine dermis (Permacol) exhibited greater tensile strength than non-crosslinked Strattice and XenMatrix throughout all levels of repetitive loading ($p<0.0001$).

Conclusions: Scaffolds such as Strattice, AlloMax, Permacol, FlexHD, and PeriGuard displayed changes in mechanical properties upon exposure to repetitive loading cycles. Scaffolds such as Strattice and AlloMax that lose strength after repetitive loading may not be appropriate for scenarios involving elevated stresses, such as patients with high BMI or when replacing large areas of the abdominal wall without tissue reinforcement.

113 **Stoker, Geoffrey E**
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Intervertebral disc disease in vitamin D-deficient spine surgery patients

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Introduction: Vitamin D metabolites elicit an anti-inflammatory response and thus potentially an anti-catabolic expression profile within the human intervertebral disc. As such, vitamin D deficiency may be a risk factor for disc degeneration, herniation, and chemical radiculitis, the combination of which annually result in multimillion-dollar healthcare expenditure and wage loss. We sought to examine the association of serum vitamin D concentration with intervertebral disc disease.

Methods: We undertook a cross-sectional study of 900 adults undergoing surgery at a tertiary-referral spine center from 1/2010 through 5/2011. Ninety-one consecutive, eligible patients had cervical magnetic resonance imaging (MRI) and a preoperative serum 25-hydroxyvitamin D measurement. MRI was read by 2 authors for C2-T1 disc degeneration (grades I-V; inter-observer k, 0.59) and herniation (inter-observer k, 0.66). Two patients (12 of 546 discs; 2%) with incomplete questionnaires were excluded from multivariate linear and logistic regression. The primary outcome measures were herniation and degeneration severity in relation to vitamin D deficiency (<20 ng/mL).

Results: Compared to 384 controls, 162 discs of vitamin D-deficient patients were more frequently herniated (40% vs 27%; *P* = .003); deficiency was not predictive of individual disc grade (unadjusted odds ratio [OR], 0.98; *P* = .82). Having adjusted for age, skin tone, body mass index, comorbidity, self-reported pain, and prior spinal injury, among other variables, deficiency was positively associated with the number of herniations per patient (adjusted OR, 2.12; *P* = .02). When discs were analyzed individually, and levels (eg, C5-C6) were additionally controlled for, deficiency conferred increased likelihood of herniation (adjusted OR, 2.06; *P* = .005).

Conclusions: Our results suggest that depleted vitamin D levels are associated with disc herniation, despite adjustment for factors that limit bioavailability and cutaneous biosynthesis of the hormone. Considering the current, coincident epidemics of vitamin D insufficiency and back pain, further investigation is warranted, as these cross-sectional observations may have substantial public health implications.

016, 017, 018 **Tang, Michael E**
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Development of novel electrospun absorbable polycaprolactone (PCL) scaffolds for hernia repair applications

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**These authors contributed equally to this work.*

Introduction: Electrospun scaffolds are a novel class of biomaterials which may provide a unique platform for the design of increasingly advanced soft tissue repair materials. Unlike currently available hernia repair materials, absorbable electrospun scaffolds possess the ability to direct cellular orientation through the presentation of ordered topographical cues and to prevent fibrosis through resorption of the scaffold. The purpose of this study was to develop a variety of electrospun meshes and to evaluate the morphological characteristics of these materials to determine their suitability for hernia repair applications.

Methods: High molecular weight (MW) and low MW polycaprolactone (PCL) were solubilized at a variety of concentrations in a 4:1 mixture of dichloromethane and N,N-dimethylformamide. These solutions were then electrospun. Flow rate, applied voltage, and needle tip to collector plate distance were altered to produce consistent scaffolds. Scanning electron microscopy was performed to evaluate scaffold microstructure.

Results: The high MW PCL solutions produced more consistent microstructures than the low MW solutions. Higher wt/vol% solution reduced the appearance of beading. Changes in flow rate did not significantly alter fiber diameters.

Conclusions: Electrospinning was utilized to develop fibrous PCL scaffolds of a consistent microstructure. Future studies will focus on parameters such as alteration of fiber diameter, cross-linking procedures, and scaffold chemistry and the influence over mechanical strength.

096 **Yang, Lauren**

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Characterization of anti-GM-CSF autoantibody associated cryptococcal meningitis

Yang LM; Rosen LB; Freeman AF; Jutivorakool K; Bennett JE; Pancholi MJ; Sampaio EP; Holland SM; Brown SK

Introduction: Anti-GM-CSF autoantibodies are an established cause of acquired pulmonary alveolar proteinosis (PAP), a severe lung disease. Although reports describe identification of opportunistic pathogens in PAP patients, many of these reports occurred before GM-CSF autoantibodies were identified and lack convincing proof of true infection. Evidence for impaired alveolar macrophage and neutrophil function have been shown in both human PAP patient blood and from GM-CSF$^{-/-}$ mouse bone marrow, suggesting patients with anti-GM-CSF autoantibodies may have increased susceptibility to pathogens. We identified three HIV-negative subjects with anti-GM-CSF autoantibodies and cryptococcal meningitis. We hypothesized that anti-GM-CSF autoantibodies in these patients were interfering with an effective monocyte/macrophage response.

Methods: A particle-based assay was used to screen patients for anti-GM-CSF autoantibodies. Flow cytometry was employed to measure cellular response to GM-CSF stimulation in the presence of patient or control plasma using phosphorylated Signal Transducer and Activator of Transcription 5(pSTAT5) as an intracellular marker of GM-CSF signaling. Downstream production of MIP-1α was measured via the Bio-plex assay.

Results: The particle-based assay revealed that the patients' plasma had titers of anti-GM-CSF autoantibodies at least 3 orders of magnitude higher than control plasma. When normal monocytes were incubated in control plasma and stimulated with either IL-3 or GM-CSF, they exhibited pSTAT5 levels similar to cells incubated in patient plasma stimulated with IL-3. However, cells incubated in patient plasma stimulated with GM-CSF had very low levels of pSTAT5 that were similar to that of non-stimulated cells. MIP-1α levels were suppressed in normal cells incubated in patient plasma, as compared to those incubated in control plasma.

Conclusions: It appears that anti-GM-CSF autoantibodies may predispose some patients to infection with Cryptococcus. Our three patients with cryptococcal meningitis have anti-GM-CSF autoantibodies that are biologically active *in vitro* at the level of signal transduction (pSTAT5) and protein expression (MIP-1α).

021 **Yozamp, Nicholas**

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Role of c-Myb in airway epithelial cell differentiation

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Introduction: Proper gene regulation in the lung is essential for the differentiation of airway epithelial cells from basal cells into ciliated and secretory types. Our lab has previously shown that transcription factor Foxj1 is necessary for the development of motile cilia, yet it does not commit a cell to the ciliated fate. The purpose of this research is to characterize the role of one possible upstream regulator of Foxj1 and of ciliogenesis that we have identified using a genetic screen: transcription factor c-Myb.

Methods: Experiments were performed in sections of embryonic mouse lung and in a primary cell culture system of mouse tracheal epithelial cells and human tracheal epithelial cells. *In vitro*, cells were proliferated then differentiated using conditions in which developmental stages are clearly defined. Over-expression and targeted deletion using viral vectors, pharmacologic cell treatments, and immunostaining were performed; experiments were analyzed via microscopy and western blot.

Results: Assessment of airway epithelial cell differentiation *in vivo* and *in vitro* shows that c-Myb is expressed prior to Foxj1, then co-localizes with it, and is extinguished when cells fully differentiate. However, in Foxj 1 knockout cells, c-Myb does not extinguish as in wild-type cells, suggesting a role in ciliated cell fate. Characterization of the c-Myb-expressing cell shows that it is distinct from the undifferentiated basal cell and also expresses the Foxj1-independent early ciliogenesis protein Cep120. Targeted deletion of c-Myb using shRNA in MTECs resulted in a decrease in ciliated cell differentiation as compared to control cells.

Conclusions: Results are highly suggestive for a role of c-Myb in early commitment of airway epithelial cells to ciliated cells. The identification of c-Myb-expressing cells which are distinct from basal cells and also express ciliogenesis proteins Cep120 and Foxj1 isolates c-Myb to the early ciliated cell. Further elucidation of c-Myb's role in the developing airway will not only facilitate knowledge of the normal lung, but will also aid in diagnosis and treatment of lung diseases in which this pathway is defective.

139 **Zhang, May**

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Gastrointestinal malabsorption contributes to weight loss in amyotrophic lateral sclerosis

Zhang M; Wills AM

Introduction: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the progressive loss of upper and lower motor neurons. Weight loss is a common problem in ALS, and is usually attributed to dysphagia, muscle atrophy, hypermetabolism, and increased respiratory function. Patients using enteral nutrition bypass several of these problems and are more weight stable. The purpose of this study is to examine whether ALS patients continue to lose weight while using EN, and which factors contribute to those weight changes.

Methods: We performed measurements on energy expenditure, body composition, disease severity, respiratory dysfunction, dietary intake, and gastrointestinal function on 10 ALS patients using enteral nutrition (EN) to evaluate what factors contribute to weight changes while using tube feeding.

Results: Patients on average ate 8% more than their caloric need, and 70% patients had positive energy balances. Nevertheless, patients lost on average -0.69 lbs±1.57 lbs between visits (27 days±9 days). In a multivariable regression model, weight loss was highly correlated with patient-reported gastrointestinal problems ($R^2 = 0.71$, $p < 0.001$). Weight, resting metabolic rate, ALS disease severity, and respiratory function also predicted weight changes to a lesser degree.

Conclusions: The results of this study suggest that ALS patients on EN are well managed by dietitians. Despite that, many do continue to display problems with weight loss, with the greatest contributing factor being gut malabsorption. This hypothesis has not been well studied in the literature. Our preliminary analysis indicate that direct testing on GI function should be done to explore the possible role of gut malabsorption in the unexplained weight loss displayed in ALS.

120 **Zhao, Peter**

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***Drosophila melanogaster* as a model organism for studying mitochondrial fusion and cardiac function**

Zhao P; Jowdy C; Dorn G

Introduction: Using *Drosophila* as the animal model, the objective is to investigate the importance of mitochondrial fusion in maintaining cardiac function. Mitochondrial fusion is mediated by 2 mitofusin proteins (hMfn1 and hMfn2), which are located in the outer membrane. The *Drosophila* homolog of the mitofusin proteins is the mitochondrial assembly regulatory factor (MARF also called dMfn). Using the GAL4/UAS system, dMfn-RNAi was targeted to the heart tube and eyes to achieve tissue-specific knockdown of dMfn and suppress mitochondrial fusion. This resulted in the development of dilated cardiomyopathy and defects in eye morphology, respectively. The data supports that mitochondrial fusion is necessary for normal heart function.

Methods: The responder line, which consisted of dMfn-RNAi and the UAS element, was separately crossed to the tincΔ4-GAL4 driver for heart tube specific knockdown of dMfn and the *ey*-GAL4 driver for eye specific knockdown of dMfn. Heart tube function was assessed using optical coherence tomography (OCT), and eye morphology was observed under a light microscope.

Results: Knockdown of dMfn in the eyes resulted in a variety of morphological defects. In addition, knockdown of dMfn in the heart tube resulted in significantly increased end diastolic dimension and end systolic dimension along with decreased fractional shortening. The OCT data shows that the suppression of mitochondrial fusion in the heart tube results in dilated cardiomyopathy.

Conclusions: The results confirm that mitochondrial fusion is an important process in maintaining normal heart function. In addition, this study demonstrates that the *Drosophila* eye can serve as a fast and useful indicator of the effects of gene manipulation. As a whole, *Drosophila melanogaster* proves to be an effective model for studying cardiac function.

Forum for International Health and Tropical Medicine

121 **Beyer, Alexander**
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Multifocal osteomyelitis in pediatric patients in New Zealand
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Introduction: Osteomyelitis in children is a relatively uncommon but serious disease. Multifocal osteomyelitis is particularly troublesome because it can appear in different sites and can cause chronic symptoms and growth arrest. This paper compares the results of treatment of acute haematogenous osteomyelitis (AHO) with that of multifocal acute haematogenous osteomyelitis in the paediatric population between November 1997 and December 2007 at Auckland's Starship and Middlemore Hospital. The emphasis of this study was to determine if Multifocal AHO differed from AHO, in any demographic, diagnostic, or clinical characteristics. If it could be differentiated from AHO the next goal was to determine if there was a difference in patient outcome.
Methods: The study population was determined by use of clinical coding at both Starship and Middlemore Hospitals. The population was then run through several exclusion criteria and then separated into an AHO and a Multifocal AHO group. Data was collected for the following variables; ethnic group, incidence and gender, laboratory markers, site of osteomyelitis, diagnostic method, length of antibiotic treatment, specific antibiotic used, and complications and outcomes of disease and treatment.
Results: Preliminary analysis found a 4.5% incidence of Multifocal AHO in the population with 37 cases out of 816 total patients. Comparison of the Multifocal AHO and the AHO populations showed similar characteristics between ethnic group, incidence and gender, and laboratory markers. The Multifocal AHO group had significantly longer periods of treatment, more surgical interventions, and a higher relapse rate.
Conclusions: Multifocal acute haematogenous osteomyelitis appears to have the same disease process as AHO and affects the same populations. It differs in that it requires longer and more invasive treatment procedures. Clinically it appears to be a more serious form of the same acute haematogenous disease process. Its higher relapse rate should be investigated to see if better treatment options are available and if it should be treated the same way as AHO.

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First characterization of IL28B polymorphisms among HCV carriers in the Brazilian population: A Latin American perspective
Araújo EAS; Melo CE; DeAndrade DS; Martins LP; Tengan FM; Barone AA
Introduction: The single nucleotide polymorphism (SNP) of interleukin-28B (IL28B) at rs12979860 has been associated with a sustained virological response in patients treated with pegylated interferon-alpha and ribavirin. This study aims to classify and evaluate the occurrence of IL28B genotypes in the Brazilian population infected with genotype 1 hepatitis C virus.
Methods: We carried out genotyping analysis by PCR to determine IL28B rs12979860 frequency and distribution among our study cohort of 500 patients. HCV viral subtype analysis was also completed using the VERSANT™ HCV Genotype Assay-LiPA.
Results: We found that heterogeneity for the C allele at rs12979860 was most common, with 59.8% of patients having genotype T/C. Only 19.8% of patients were found to have genotype C/C. T/T was found in 20.4% of our cohort. In our retrospective study, no association between rs12979860 genotype and race was found (P=0.553). Results showed a higher prevalence of genotype 1b compared to genotype 1a (55% vs. 32.4%). This is relevant given that genotype 1b has a higher genetic barrier to resistance to the new HCV protease inhibitors.
Conclusions: Our study characterizes the current state of chronic genotype 1 hepatitis C infection in the Brazilian population in anticipation of new Direct Antiviral Agents, which are likely to depend on host and viral factors for their success. Most of our population has the worst profile (20.4% T/T and 59.8% T/C). For these individuals, a regimen containing interferon alpha, ribavirin and a protease inhibitor may pose a risk of selecting resistant HCV mutants. These patients would require more frequent and careful viral load monitoring during the protease inhibitor phase of therapy. No racial differences were observed regarding IL28B genotype among Brazilians. Genotype 1b was the most prevalent among this Brazilian population, which is favorable in terms of the genetic barrier to protease inhibitor resistance.

032 **Fjeldstad, Heidi E**

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10-year follow-up of adolescents with familial hypercholesterolemia following participation in statin trials

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Introduction: Familial Hypercholesterolemia (FH) is a genetic disease in which a reduced number of LDL receptors causes elevated cholesterol levels from birth. Early, life-long treatment ameliorates excess cardiovascular disease (CVD) risk due to FH. In 2000/2001 two clinical trials, one comparing simvastatin vs placebo, the other comparing atorvastatin vs placebo, were performed to determine the efficacy and safety of statins in treating adolescents with FH. The present study aims to investigate treatment and quality of life of the study participants over the past >10 years.

Methods: All patients from Norway who participated in the clinical trials were or will be contacted. Patients were 12-17 years old during the clinical trials. Out of 37 patients asked to participate, 25 have completed this follow-up study. Patient interviews were conducted by a medical student. Current lipid and lipoprotein levels were measured by blood test. Other data was collected from patient journals. Participation in the study was voluntary and based on written consent. The study was approved by the Regional Ethics Committee in Norway.

Results: Average time from trial completion to next FH appointment was 1.6 (0.2 – 8.0) years. Subsequent follow up for FH has been ≥ every other year for all but 2 patients. 17 patients (68%) reported gradually decreasing cholesterol values (on treatment over the last 10 years); only one reported increasing values. The majority (61%) agreed that they wished they did not have to worry about lifestyle due to FH. None of the participants wished their families did not know about the FH diagnosis or that they had been diagnosed with FH later in life. 48% agreed either completely or partially that they worry about developing CVD as a result of having FH.

Conclusions: Though the majority of patients in this study have received consistent follow up since childhood with treatment that has lowered their cholesterol levels, many of these patients still worry about developing CVD as a result of their FH. It should be possible to alleviate these worries since evidence has shown that treating FH ameliorates the added risk of CVD conferred by FH.

094 **Jin, Linda**

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Male circumcision campaign in Iringa, Tanzania: Matching demand, quality and efficiency in a high volume setting

Jin L; Chrouser K

Introduction: The World Health Organization and UNAIDS has recommended male circumcision (MC) as one of the key HIV/AIDS prevention interventions based on studies that show a 60% reduction in transmission of HIV infection during heterosexual sex in males who are circumcised versus those who are not. This campaign aimed to circumcise 10,000 men aged 10 and up during a 4 week campaign in the Southern Iringa region.

Methods: Eleven circumcision sites were established at regional and outreach health centers in the Southern Iringa region of Tanzania between June 20, 2011 and July 15, 2011. Demand creation in local towns and villages began two weeks prior to the campaign launch, and continued throughout. All clients were provided the standard WHO HIV package, including testing and counseling, in addition to an optional medical circumcision with 2 and 7 day follow-up exams.

Results: Although the campaign target was to circumcise 10,000 clients in four weeks, the demand exceeded expectations, and the campaign was extended from July 15, 2011 to August 11, 2011, and the total number of clients circumcised was 20,846. The adverse event rate was <0.5%. Of 99.7% of clients that opted for HIV testing, 1.07% positive for HIV, although the rate jumps to 17.9% when only considering the 35 and up age category. Major challenges identified during the campaign included procuring and distributing surgical supplies, balancing regional demand and medical and human resources, lack of electricity and difficulty with transportation, and maintaining health provider morale.

Conclusions: The results of this campaign were extremely positive, and the target client number was exceeded by over 100%. The Iringa experience shows the campaign mode of service delivery is capable of delivering quality male circumcisions services at volume even in rural settings, without compromising client safety.

028 **Kim, Aram**

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The effect of Metformin on the recurrence of polyps after colorectal polypectomy in DM patients

Kim A; Han M; Kim T

Introduction: Metformin, a common first line drug for treatment of type 2 Diabetes, has recently been associated with a possible preventative effect on recurrence of colorectal diseases. The purpose of this study is to explore the relationship between Metformin and the recurrence of colorectal polyps after colorectal polypectomy in DM patients.

Methods: 269 patients were selected from the hospital database based on the following criteria: type 2 Diabetes, colorectal polypectomy with at least 1 follow up colonoscopy 1 year after. 2X2 and chi squared tests were performed.

Results: Based on preliminary statistical analysis, there seems to be no apparent correlation with Metformin intake and the recurrence rate of colorectal polyps after polyps had been removed once. Further statistical analysis looking at subgroups is warranted and will be conducted. It is anticipated that there will be a significant decrease in the recurrence of polyps of those DM patients that take Metformin in comparison to those that take another diabetes drug.

Conclusions: The impact of this research on the type 2 Diabetic or colorectal disease population would be tremendous as the two populations have a large overlap. If one drug could treat one disease while preventing another that is closely associated with the first, it would be efficient not only pharmacologically but also financially for the patient as well as the medical industry. Furthermore, as most colorectal malignancies arise from polyps, a decrease in the growth of polyps could be used as a direct measure of colorectal cancer prevention.

037 **Marshall, Brigid**

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Validation of non-invasive hemoglobin measurement at high altitude in Puno, Peru

Marshall B; Checkley W

Introduction: One of the most common fatal altitude-related illnesses is Chronic Mountain Sickness (CMS), characterized by excessive polycythemia and increased blood viscosity. This project sought to determine whether non-invasive hemoglobin assessment with the Masimo Pronto and Pronto 7 devices is a valid approach for the identification of individuals with CMS in a high altitude setting. Specifically, the project compared hemoglobin measurements acquired with the Pronto and Pronto 7 devices to the traditional invasive cyanomethmoglobin method of hemoglobin measurement amongst high altitude residents in Puno, Peru.

Methods: All measurements were conducted in Puno, Peru, at an altitude of 3825m. Hemoglobin concentration of each participant was measured using the traditional invasive cyanomethemoglobin method. The concentration was also measured with either the Pronto or Pronto 7 device. 41 individuals were tested with the Pronto and 23 individuals were tested with the Pronto 7. Two participants from each group were polycythemic (Hb >19 g/dL for females, Hb>21 g/dL for males). The data from the noninvasive device was compared to the invasive data using the Bland-Altman approach.

Results: The average bias of the readings of the Pronto device was -1.10g/dL. The standard deviation of the difference between the two methods was 1.14g/dL, therefore limits of agreement around the average bias are -3.33 g/dL to 1.13 g/dL. The average bias of the readings of the Pronto 7 device is -.652g/dL. The standard deviation of the difference between the two methods is 1.22g/dL, therefore limits of agreement around the average bias are -3.04 g/dL to 1.74 g/dL.

Conclusions: The initial analysis of the Pronto 7 measurements suggest accuracy at high altitude similar to that found at sea level. Therefore, the Pronto 7 could potentially provide a rapid and cheap assessment of the overall prevalence of CMS in Puno, Peru. However, further data needs to be collected in order to verify the results and provide more information on the device accuracy with polycythemic patients.

030 **Orth, Heather N**

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Using the 6 minute walk test to investigate chronic mountain sickness severity in Puno, Peru

Orth H; Checkley W

Introduction: The 6 Minute Walk Test (6MWT) is an easily performable test used to evaluate functional exercise capacity in patients with pulmonary and cardiac conditions. Given the significant pulmonary complications of chronic mountain sickness (CMS), the 6MWT may be a strong candidate for preliminary evaluation of CMS severity. The purpose of this project is to determine whether a decreased 6MWT distance correlates with CMS severity in CMS patients in Puno, Peru as compared to normal healthy control participants from the same area.

Methods: Participants in a larger, 3 year long, NIH funded epidemiological study of chronic diseases in Puno, Peru were identified as possible candidates for participation in this project for both the CMS and normal, healthy control groups. The 6MWT was performed with only slight modifications to the established American Thoracic Society guidelines.

Results: Due to logistical complications, the results of the project preclude any conclusive statistical analysis.

Conclusions: CMS prevalence in Puno, Peru may be lower than previously expected, but the 6MWT is a test that can be relatively easily performed in a setting lacking some advanced research resources and could be an advantageous test where traditional cultural beliefs are often obstacles to more invasive testing for CMS. Future research is needed to better determine whether CMS severity correlates to a decline in 6MWT distance.

137 **Reinhardt, Samuel**

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Characterization of the *Strongyloides ratti* excretory/secretory product

Reinhardt S; Mulvenna J; McCarthy JS

Introduction: *Strongyloides stercoralis* is a human intestinal parasite in the category of neglected tropical diseases. Diagnosis presents a particular challenge, and stool microscopy remains insensitive. *Strongyloides* can cause lifelong infection, implying a unique ability to modulate the host immune system to allow its persistence in the intestines. The objectives of this project were to isolate the excretory/secretory product (ESP) of *Strongyloides ratti* and characterize it through tandem liquid chromatography mass spectroscopy (LC-MS/MS) analysis. *S. ratti* is a rat parasite and model organism that closely resembles the *S. stercoralis* infection in humans, and was used to successfully develop the coproantigen test in the McCarthy lab. The hope is that the characterization of the ESP will enable development of more specific and sensitive diagnostic assays, and give insight into how *Strongyloides* causes infection and remains in the host for such long periods of time.

Methods: *S. ratti* parasitic worms were isolated from infected rats and cultured to collect excretory/secretory product (ESP). ESP was concentrated and buffer-exchange dialyzed, then subjected to SDS-PAGE and in-gel tryptic digests. Peptides were extracted and run on tandem liquid chromatography mass spectroscopy (LC-MS/MS), and spectra analyzed by comparing with Mascot and Nematoda databases, as well as De Novo peptide searches.

Results: At time of submission, the two samples run with LC-MS/MS yielded spectra with no peptides amenable to analysis. Further samples are awaiting analysis, pending the resolution of technical difficulties with the mass spectrometer.

Conclusions: At the time of submission, the lack of results precludes any definitive statements about this project's significance. However, we are optimistic that our ESP analysis will eventually yield results amenable to analysis. These results will give novel insight into the secretome of *S. ratti* and how it is able to cause long-term infection in the host. Additionally, a characterized secretome will allow for more specific development of diagnostic tests for human infections by *S. stercoralis*, which to date remain poorly sensitive.

Fogarty International Clinical Research Scholars Program

034 **Painschab, Matthew**

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Biomass fuel exposure increases cardiovascular disease risk in a Peruvian Andean population

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Introduction: Globally, about 90% of rural households use biomass fuels for cooking. Biomass fuel use increases the risk of pneumonia, tuberculosis, COPD, and all-cause mortality. In the Peruvian Andes, the use of biomass fuels in rural populations is essentially exclusive. Evidence is lacking on how biomass fuels effect cardiovascular diseases. Carotid ultrasound for cholesterol plaque and carotid intimal medial thickness is a well-validated, inexpensive, non-invasive surrogate marker for future cardiovascular events. The purpose of this study is to evaluate the effect of biomass fuel exposure on atherosclerotic burden via carotid ultrasound.

Methods: The study took place in Puno, Peru at 3825 meters above sea level. We sought to enroll patients age $\geq$ 35 in two groups: urban patients who cook with gas stoves and rural patients who cook with wood or cow dung. A questionnaire and clinical evaluation were administered to all participants to assess cardiovascular risk factors, and all patients had an ECG, carotid ultrasound, and echocardiogram.

Results: Carotid artery plaque was significantly more prevalent in the population exposed to biomass fuels, RR 1.75 (95% CI 1.21-2.54). This difference was more pronounced among females, RR 2.13 (1.34-3.39). There was a significantly significant difference in males <55 yo; RR 4.51 (1.88-10.80) but not among the male population as a whole RR 1.42 (0.78-2.60).

Conclusions: The effect of biomass fuels on atherosclerosis and CMS has not been studied previously. This study demonstrates a striking effect of biomass fuel exposure on atherosclerosis. First, it demonstrates that ultrasound use is feasible in low resource area for both research and practice. Also, this was a cross sectional population wide study with similar genetic admixtures, limiting confounders. Limits of this study include the use of a surrogate marker for CVD as well as socioeconomic differences in groups. Full statistical analysis and longitudinal studies should now be conducted to evaluate the disease burden from CVD in this population as well as how interventions may decrease exposure.

MA/MD Program

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Mentor: Audrey Odom, MD, PhD

Validation of IspD as a target for novel antimalarial drug development

Masters MC; Odom AR; Armstrong C; Hodge D

Introduction: New therapies are needed to treat severe *Plasmodium falciparum* malaria. Globally, the human malaria parasite, *P. falciparum*, is responsible for significant morbidity and mortality, particularly in children under the age of five years. Exacerbating this substantial burden, resistance to all major classes of antimalarial drugs is widespread. Methylerythritol phosphate cytidyltransferase (IspD) - the second dedicated enzyme in *P. falciparum's* essential isoprenoid biosynthesis pathway - offers a putative target for novel antimalarial drug development. We propose to validate that IspD is essential to the intraerythrocytic growth and development of *P. falciparum* parasites.

Methods: To ascertain the essentiality of IspD in *P. falciparum*, IspD under- and over-expressing parasite strains will be engineered. In IspD knockout and knockdown models, rates of cell cycle arrest will assess survival and mass spectrometry will quantitate the metabolites of the *P. falciparum* isoprenoid biosynthetic pathway. In IspD over-expressing strains, IC_{50}s (50% inhibitory concentration) for fosmidomycin - a known inhibitor of isprenoid biosynthesis in *P. falciparum* - will determine drug resistance. The over-expressed protein will also be localized within the parasite using both GFP and antibody tagging methods.

Results: We expect that IspD will be essential in *P. falciparum.* As such, complete IspD knockout is putatively parasite lethal. An IspD knockdown model of the *P. falciparum* parasite will allow for conditional IspD expression. Thus, if IspD is essential for *P. falciparum* isoprenoid biosynthesis, parasite lines with reduced or absent IspD expression will phenocopy fosmidomycin-treated wild type *P. falciparum.* Moreover, if IspD is a fosmidomycin target - and thereby a target for parasitic isoprenoid biosynthesis inhibition - overexpression of this protein is predicted to confer resistance to the drug, evidenced by an increase in IC_{50} (50% inhibitory concentration). IspD is expected to be apicoplast-localized due to its N-terminal leader sequence.

Conclusions: The data resulting from these studies will determine IspD's validity as a target for development of novel antimalarial chemotherapeutic agents. Preliminary work in the Odom lab has purified the IspD enzyme recombinantly in *E. coli*. Pending IspD's validation as an antimalarial drug target, high throughput screening of the IspD protein against large chemical compound libraries could help identify new enzyme inhibitors. These inhibitors would represent lead compounds for future antimalarial drug development.

Radiological Society of North America (RSNA)

061 **Mityul, Marina**
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Mentor: Tammie Benzinger, MD, PhD
Biomarkers of pre-clinical Alzheimer's disease using MRI and PET
Mityul MI; Benzinger T
Introduction: Amyloid plaques, the hallmark of AD pathology, can be detected in the brains of asymptomatic people using PiB PET, but individuals' risk and time course are unclear. Arterial spin labeling is an fMRI measurement of cerebral blood flow, which is altered in the diseased areas of AD patient's brains. The purpose is to correlate regional PiB uptake and evaluate the utility of ASL as a biomarker of pre-clinical AD. The hypothesis is that early in pre-clinical AD, areas of the brain with early amyloid deposition will have inflammation and increased cerebral blood flow.
Methods: Cognitively normal subjects enrolled at the Alzheimer's Disease Research Center Adult Children Study underwent PET and ASL studies on a Siemens 3T Trio scanner. FreeSurfer, an automated brain reconstruction tool, was used for segmentation. We examined correlation between PiB binding potential with volumetrics and cortical thicknesses, averaged across subjects for group analysis using QDEC. After image registration, each FS region of interest will be used examine cerebral blood flow as a function of amyloid plaques.
Results: We analyzed 55 subjects, 11 of whom were PIB positive (mean cortical binding potential ≥ 0.18) suggesting greater amyloid deposition. There were statistically significant differences in several volumes including the caudate, but not in the cortical thicknesses of the 7 regions studied. The CBF was greater in PIB+ subjects in nearly all ROIs but the difference in means was only statistically significant in the parahippocampal gyri.
Conclusions: Analysis will correlate baseline CBF with cortical amyloid load as assessed by PET as well as status, CSF biomarker status, and neuropsychological measures. By integrating advanced measures of brain structure and function with conventional volume measures, biochemical changes of Aβ deposition and behavioral measures, the early pathophysiology of AD may be examined. Longitudinal data will yield insights into pathophysiology, combined methods for diagnosing and staging AD, and ultimately aid in prevention.

066 **Strother, Marshall C**
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Mentor: James Duncan, MD, PhD
Radiation use during fluoroscopic procedures as a quality measure
Strother MC; Street M; Duncan JR
Introduction: The rapid growth of medical imaging has led to concerns about the long term consequences of exposing large numbers of patients and healthcare workers to increasing levels of ionizing radiation. The goal of this project was to develop a method of continuous, quantitative, and automated monitoring of physician performance and radiation usage during procedures.
Methods: Development of a custom software package which performs a variety of simple analyses on radiation usage data extracted from billing records and DICOM Structured Reports. (Software is available as open source at http://code.google.com/p/dicom-sr-qi/)
Results: Key metrics tracked by our software include: average frames per second of pulsed fluoroscopy, usage of different imaging modalities, identification of cases exceeding a specified dose threshold and the factors contributing to dose in these cases, and a novel performance metric which aggregates pedal times meaningfully across different procedure types. These reports have been used to meet requirements for ongoing physician practice evaluation and drive dose reduction efforts internally at the Mallinckrodt Institute of Radiology. Differences between physicians generally correlated with levels of experience. Comparisons between hospitals revealed opportunities to significantly reduce dose by changing default machine settings, imaging pulse rates, and usage of different intra-operative imaging modalities.
Conclusions: Semi-automated tracking of physician performance and radiation usage in image-guided procedures is feasible and immediately useful. Further work is needed to validate custom metrics and to quantitatively evaluate the utility of all measures in quality improvement initiatives.

T32 NIH NHLBI Cardiovascular Biology Training Program

134 **Caputa, George**

T32 NHLBI Cardiovascular Biology Training Program
Molecular Cell Biology Program
Division of Biology and Biological Sciences
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Mentor: Jean E. Schaffer, MD, PhD

RNASET2 and lipotoxicity: Linking snoRNA processing to palmitate-induced cell death

Caputa G; Zhao S; Schaffer JE

Introduction: In obesity and diabetes, high levels of serum lipids can become deposited in non-adipose tissues, with serious consequence. Lipotoxic levels of free fatty acids can overwhelm cells, leading to cellular dysfunction and eventual cell death. However, the molecular mechanisms of this response are poorly understood.

Methods: In order to identify players in the lipotoxic response, a mutagenic screen was performed using Chinese hamster ovary (CHO) cells in which palmitate-resistant mutants were selected.

Results: A mutant cell line, 2B1, shows resistance to death in response to high levels of the saturated fatty acid palmitate. The provirus integrated in the locus for RNASET2, an endoribonucleases of the T2 family, causing haploinsufficiency of the RNASET2 protein. Complementation and independent shRNA knockdown confirms that RNASET2 contributes to lipotoxic response. 2B1 cells also fail to accumulate the non-canonical rpL13a small nucleolar RNAs, which have been shown to be critical to the lipotoxic response.

Conclusions: We conclude that RNASET2 is necessary for lipotoxic cell death, possibly through the maturation or regulation of the rpL13a snoRNAs. Future directions include understanding the exact relationship between the rpL13a snoRNAs and the elucidation of the role of RNASET2 in the context of lipotoxicity. Understanding the unique biology of RNASET2 could lead to possible preventative therapies for metabolic syndromes.

010 **Cheng, Jeffrey K**

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Department of Cell Biology, Washington University in St. Louis School of Medicine
Mentor: Robert Mecham, PhD

A fiber-based constitutive model predicts changes in amount and organization of matrix proteins in the mouse aorta

Cheng, JK; Wagenseil, JE; Mecham, RP

Introduction: Decreased elastin is associated with several human genetic diseases that result in abnormal development of the vasculature. Mouse models with elastin deficiency exhibit a functional vascular system with elevated blood pressure and increased arterial stiffness. It is important understood how the normal development process is modified to produce a mechanically functioning vascular system despite a deficiency in elastin.

Methods: We have gathered mechanical data from wild-type and *Eln+/-* mouse aorta at various ages of postnatal development ranging from day 3 to day 60. A microstructurally motivated fiber-based constitutive relation was used to fit the data with different constraints, and specific model parameters were assigned to represent protein constituents in the vessel wall.

Results: The models show an increase with age in the parameters C_1 (representing elastin) and C_4 (representing collagen) in both genotypes, with C_1 being significantly reduced at all ages in *Eln+/-* compared to WT. This agrees with previously published gene expression data that report elastin and collagen expressions peak at around P21 before returning to baseline levels. It is also been shown that elastin amounts in adult *Eln+/-* aorta are be approximately half that of WT. Taken together, this shows that the models are capable of capturing differences in protein amount in the aortic wall. The models also predict collagen fibers shifting from an axial orientation to a more circumferential orientation through a decrease in the fiber angle α with time. This remains to be verified through histology or multiphoton imaging. In addition, a second method of constraining the model separates mechanical the contributions of elastin and collagen to different effective pressure ranges. This yielded similar results, suggesting total reliance on elastin at physiological pressures.

Conclusions: Mathematical modeling can be used to predict changes in matrix protein organization and amount to guide future investigations into developmental remodeling and treatments for human disease.

011 **Jinn, Sarah**

T32 NHLBI Cardiovascular Biology Training Program
Division of Cardiology
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Mentor: Daniel S. Ory, MD

Regulation of cholesterol homeostasis by the non-coding snoRNA U17

Jinn S; Dudley NR; Schaffer JE; Ory DS

Introduction: Cholesterol is required for the growth and viability of mammalian cells, and is a critical determinant of the structure and biochemical properties of the plasma membrane. Under physiological conditions, cellular cholesterol level is governed by sterol-regulated transcriptional pathways. The trafficking pathways responsible for cholesterol homeostasis that prevents the alteration to pathophysiological conditions, however, are poorly understood.

Methods: To gain insight into the molecular mechanisms underlying these homeostatic pathways, loss-of-function mutagenesis screen was conducted in Chinese hamster ovary (CHO) cells to select for cells with defects in transporting low-density lipoprotein (LDL)-derived cholesterol from the plasma membrane to internal membranes.

Results: One of the mutants, I5, is protected from amphotericin-induced cell death. Esterification of the plasma membrane derived cholesterol in I5 is lower than wild-type CHO cells, suggesting reduced trafficking of free cholesterol to ER membranes. Provirus had integrated into one of two expressed alleles of Snhg3, which is consistent with a model of haploinsufficiency. Within the introns we identified U17a and U17b, orphan H/ACA snoRNAs that are highly conserved. Complementation experiments and recapitulation of mutant phenotype in murine system demonstrated that U17 snoRNAs but not Snhg3 mRNA is responsible for the cholesterol trafficking defect observed in mutant I5. S1 mapping showed that deficiency of U17 snoRNA does not affect the processing of 18S rRNA, a previously characterized function of U17 homolog in yeast.

Conclusions: We conclude that the U17 snoRNAs modulate intracellular cholesterol trafficking by regulating the genes that are involved in cholesterol homeostasis. The project will further explore the targets of this novel small RNA-dependent pathway, which represents a previously unrecognized mode of regulation for cellular cholesterol homeostasis. Elucidation of the mechanism by which the U17 snoRNAs exert their effects may identify new targets for treatment of atherosclerosis and other acquired states of cholesterol pathophysiology.

012 **Lee, Urvi, PhD**

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Mentors: Richard B Schuessler, PhD; Jeanne M Nerbonne, PhD

The ionic remodeling in the right atrium of a canine inflammation model of postoperative atrial fibrillation

Lee US; Fedorov VV; Schuessler RB; Efimov IR; Yamada KA; Nerbonne JM; Daminao RJ Jr

Introduction: Postoperative atrial fibrillation (POAF) is one of the major sources of morbidity following cardiac surgery. Approximately 30% of patients undergoing cardiac surgery have POAF with maximum frequency occurring around 48-72 hours after surgery. Current understanding of POAF is limited to clinical studies evaluating the effects from a variety of antiarrhythmic therapies and epidemiologic studies describing incidences and risk factors. The purpose of this study is to determine the role of inflammation as a causative factor in POAF by studying the changes in action potential and ionic currents in a surgical canine model of POAF.

Methods: A canine inflammation model was created by surgically ablating the right atrium. The dogs were survived for three days. At the conclusion of the study, optical mapping was performed, and quantitative PCR was carried out on atrial tissue to evaluate changes in ion channel and gap junction gene transcripts. Finally, whole cell recordings were used to measure ion current densities of the right atrium.

Results: The action potential duration (APD) of the inflammation group was prolonged at slower heart rates. At faster rates, there was reduction or similar APD compared to control groups. Inflammation also slowed conduction and increased restitution compared to the control group. Sodium, calcium and I_{TO} potassium channel gene transcripts were reduced in the inflammation model. However, administration of steroids dampened these changes. We anticipate that results from the whole cell recordings will reflect these changes in ion current densities between the two groups.

Conclusions: Inflammation was associated with a significant change in the electrophysiological characteristics of the canine atria. These findings are preliminary since we are trying to develop a mechanistic framework to correlate inflammation to the remodeling of the electrophysiological substrate. The results from this work will allow for the development of a targeted therapy for the prevention of POAF.

039 **Mydock, Laurel K, PhD**

T32 NHLBI Cardiovascular Biology Training Program
NIH Cardiovascular Pharmacology Training Program
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Mentor: DF Covey, PhD

The synthesis and evaluation of specific oxysterol derivatives as potential regulators of the hedgehog signaling pathway

Mydock L; Krishnan K; Nachtergaele S; Rohatgi R; Covey D

Introduction: Hedgehog (Hh) signal transduction has been found to be essential for both embryonic development and organ repair and maintenance. Serious health complications can arise from the improper function of this biological pathway, including: severe birth defects, Gorlin's syndrome (a familial cancer syndrome), and other sporadic cancers. Thus, the Hh signaling pathway represents an ideal therapeutic target for cancer-treatments and regenerative medicines. It is therefore critical to understand the intracellular mechanisms involved in this biological pathway, as many of the specific interactions are not well understood at a biochemical level.

Methods: The focus herein, is to pinpoint the specific interactions responsible for Hh signaling by exploiting the ability of oxysterols to activate the Hh pathway. By chemically synthesizing oxysterol derivatives, we aim to: *1)* Elucidate the structural elements essential for biological activity; *2)* Gain a better structural understanding of the target receptor; *3)* Characterize binding interactions (lipid perturbation vs. protein binding); *4)* Locate the specific biological target of oxysterol activation.

Results: After the evaluation of several regioisomers, we found *natural*-20(S)-hydroxycholesterol (*nat*-20(S)-OHC) to be the most potent Hh pathway activator, and have determined which sites on the molecule will tolerate structural modification. Through the use of enantiomers, we have also found that activation of this pathway by oxysterols, occurs through protein binding interactions, and are currently working on locating the specific target.

Conclusions: Upon conclusion of this systematic investigation, we will understand a mechanism by which Hh signal transduction is regulated. It is anticipated that in defining the essential structural components and identifying specific biological targets within the pathway, we will be able to modulate this pathway. This will facilitate Hh-based drug development, and provide unique approaches to cancer-therapies as well as regenerative medicines.

033 **Olsen, Brett, PhD**

T32 NHLBI Cardiovascular Biology Training Program
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Mentor: Daniel Ory, MD

Oxysterol perturbation of membrane structure

Olsen BN; Schlesinger PH; Baker NA; Ory DS

Introduction: Regulation of cholesterol homeostasis is essential to mammalian cell function, and multiple response pathways are responsible for maintaining stable cholesterol levels. Oxysterols, oxygenated derivatives of cholesterol, serve as messengers in these pathways, but the mechanisms through which they signal are still unclear. We believe that oxysterol perturbation of membrane structure can act as a signal, and we wish to identify structural perturbations that may be associated with signaling.

Methods: We use molecular dynamics simulations of phospholipid/sterol membrane bilayers to obtain atomic-level detail of how the dynamic structure of membranes is perturbed by oxysterols and identify putative signaling mechanisms.

Results: We found that side-chain oxysterols perturb membrane structure in ways significantly different from cholesterol. While cholesterol induces membrane condensation and ordering, oxysterols cause membrane expansion and disordering. These changes are likely linked to the different preferred orientations of cholesterol and oxysterols within the membrane, with oxysterols adopting a wide range of disordered and solvent-exposed conformations. Further, in membranes containing both oxysterols and cholesterol, cholesterol was found to become significantly more exposed to solvent and partially shift out of the membrane. This is consistent with the observed activation of cholesterol by oxysterols, causing it to become more available to various cholesterol-binding enzymes.

Conclusions: We have identified two putative oxysterol signaling mechanisms mediated by changes in membrane structure: large-scale disordering and expansion of membranes, which could alter the behavior of membrane-bound proteins, and activation of cholesterol in oxysterol-containing membranes, which could enhance the interaction of cholesterol with various binding or sensing proteins. These results demonstrate that cellular membranes are active and responsive components of the cellular regulatory machinery. Future research will focus on validation of these simulated results with results from biochemical and spectroscopic experiments and further examination of related sterol derivatives using similar techniques.

079 **Skinner, James R, PhD**

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Mentor: Nada A Abumrad, PhD

Obesity related CD36 mutants: expression and glycosylation

Skinner JR; Abumrad NA

Introduction: In humans, CD36 has been linked to lipid metabolism abnormalities, insulin resistance and inflammation. CD36 is a transmembrane protein that recognizes long chain fatty acids and lipoproteins. The purpose of this study is to examine the expression and subcellular trafficking of seven novel rare human variants of CD36 identified by sequencing this gene in a population of extremely obese and type 2 diabetic subjects.

Methods: Mutant forms of human CD36 were expressed in tissue culture cells, imaged by immunofluorescence to determine subcellular location, and analyzed by Western blotting for size and glycosylation status. Cell surface localization was also assessed by biotinylation.

Results: A number of human CD36 mutants, each expressing a single amino acid change, are unable to be expressed correctly at the cell surface. These mutants fail to undergo correct folding and glycosylation, and as a result do not traffic out of the endoplasmic reticulum. Several of these mutations are in specific amino acids that are conserved across species. Certain other mutants, however, do produce correctly sized proteins that are located at the plasma membrane.

Conclusions: The possible contribution of these human CD36 mutations to obesity and diabetes can be better understood by an analysis of the location of the mutant proteins. These mutants demonstrate that changes to single amino acids can result in incorrect glycosylation and trafficking of CD36. The lack of cell surface localization of these mutants suggests that certain human CD36 variants will be unable to function correctly in lipid transport.

T32 NIH Otolaryngology Training Grant

084 **Chen, Athena L**
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Summer Research Program
Department of Otolaryngology, Washington University in St. Louis School of Medicine
Mentor: Timothy E. Hullar, MD
Audio-vestibular temporal binding window in healthy, elderly subjects
Chen AL; Malone AK; Chiang LY; Smith SB; Wong KS; Chang NN; Hullar TE
Introduction: As we age, the way we judge coincidence of multisensory stimuli changes. That this affects our balance – specifically, our propensity to fall or not to fall – has been proposed. In this study, we use the temporal binding window (TBW) for auditory and vestibular stimuli to measure multisensory integration in healthy, elderly subjects. We compare their TBWs with those of healthy, young subjects.
Methods: Two experimental paradigms were used. Subjects were seated in a sinusoidally-rotating chair and wore headphones that delivered sounds at different time delays or phase shifts with respect to the chair movement. Responses as to whether or not the stimuli presented were simultaneous/aligned were used to calculate TBWs. Clinical tests of balance, the Timed Up and Go (TUG) test and Clinical Test of Sensory Organization and Balance (CTSIB), were administered.
Results: Previously, the TBW for healthy, young subjects was found to be 147 msec (±46 SD or ±23 SEM). Using the same experimental setup, we found an average TBW of 366.6 msec (±186.3 SD or ±76.1 SEM) in a group of healthy, elderly subjects. By another audio-vestibular paradigm, the TBW for healthy, young adults was 343 msec (±85 SD or ±35 SEM); by comparison, it was 581.6 msec 596.9 msec (±164.0 SD or ±54.7 SEM) for a different group of healthy, elderly subjects.
Conclusions: The results of this study indicate that the TBW of audio-vestibular stimuli is significantly widened in older adults. The two paradigms used are not immediately comparable to each other; however, the results obtained using both methods support the same conclusion.

080 **Chiang, Leslie Y**
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Audio-vestibular temporal binding window in healthy, young subjects
Chiang LY; Smith SB; Wong KS; Chen AL; Chang NN; Hullar TE
Introduction: The integration of cues from multiple sensory streams allows us greater certainty in interacting with and responding to stimuli from the environment. Signals from different sensory modalities may be perceived as originating from the same event yet do not arrive at the brain simultaneously, meaning there exists a certain tolerable window of time in which the signals can be perceptually bound together. Previous paradigms used to investigate the audio-vestibular temporal binding window used brief raised-cosine trajectories as a vestibular stimulus. However, these experiments had to correct their data by taking into account the time that the rotational stimulus took to reach vestibular perceptual threshold. The method of using only brief raised-cosine stimuli paired with 10-ms tones may also be too unlike lifelike stimuli to yield data that would have practical therapeutic implications.
Methods: In this study, we use a method of continuous vestibular stimuli, which bypasses the need to adjust experimental data for the time needed to reach the vestibular threshold. The experimental task of determining the alignment of contralateral stimuli is also more representative of real world situations involving moving sound sources and head rotation.
Results: We investigated the perceived timing relationships between vestibular and auditory stimuli in healthy, young adult subjects with no history of vestibular or auditory disease.
Conclusions: Characterizing these parameters in healthy adults allows us to compare these data to target patient populations such as the elderly, who experience age-related changes in sensory processing, and in patients with vestibular disease that predispose them to falls. Information on how central processing integrates information streams from different sensory modalities may be of therapeutic benefit.

087 **Perez, Philip**

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Mentor: Jianxin Bao, PhD

The aging inner ear: a role for glucocorticoid receptors and related enzymes

Perez PL; Bassuner R; Zhou H; Lei D; Bao J

Introduction: Glucocorticoids carry out a broad array of biological functions as steroidal hormones that mediate response to stress. Among their effects, glucocorticoids have been shown to have a profound impact on neuronal function. In the cochlea, activation of glucocorticoid signaling pathways provides protection from noise-induced hearing loss, and indirect evidence suggests the involvement of glucocorticoids in age-related loss of spiral ganglion neurons. Given the major public health concerns posed by both noise-induced and age-related hearing loss, dissecting the role of glucocorticoids in these processes could open major avenues for treatment and prevention. Hampering a better understanding of the signaling mechanisms of these hormones in the cochlea, however, is the incomplete information on their receptors and related enzymes.

Methods: In situ hybridization was used to examine the expression pattern of glucocorticoid receptor, mineralocorticoid receptor, 11β-HSD1, and 11β-HSD2 in the mouse cochlea, and quantitative RT-PCR was employed to assess any changes in the presence of these molecules associated with aging.

Results: We mapped the specific expression pattern of the above molecules in the cochlea and confirmed their continued presence in the aged mouse cochlea.

Conclusions: Based on these newly discovered expression patterns, we can speculate that the mineralocorticoid receptor is critical for glucocorticoid signaling in spiral ganglion neurons, the spiral ligament, and the stria vascularis under normal conditions. After noise exposure or during aging, the glucocorticoid receptor may play a key role in glucocorticoid signaling in spiral ganglion neurons and the spiral ligament. Thus, this work implicates GR signaling in the aging cochlea and establishes a framework for further dissecting this role and its possible link to age-related hearing loss.

132 **Zieske, Lawrence**

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Mentor: Susan Mackinnon, MD

Evaluation of nerve injection injury

Zieske L; Bery A; Laurido-Soto OJ; Johnson P; Hunter D; Mackinnon S

Introduction: Nerve blocks are commonly performed for pain control during surgical procedures and for alleviation of chronic pain. Currently, there is a debate whether injection of local anesthetics into peripheral nerve causes functional damage. Numerous studies have shown that intrafascicular injection of nerve block agents causes significant axonal destruction. Reports of iatrogenic injuries from nerve blocks are significant and include severe hyperalgesia. This study aims to replicate the findings of past experiments which showed that injection of local anesthetics causes damage to peripheral nerve.

Methods: Adult male Lewis rats will be randomly assigned to ten experimental groups. Normal saline (negative control), 10% phenol (positive control), 0.5% ropivacaine, 0.5% bupivacaine, or 1% lidocaine will be administered by intrafascicular injection or extrafascicular injection into the left tibial nerve. At 14 days after the injection, we will perform muscle tetanic force measurements to assess functional damage, and we will harvest the injected nerve to assess histomorphologic damage using light microscopy.

Results: A recent study reported that intrafascicular ropivacaine injection does not cause a functional deficit to the innervated muscles. The study evaluated functional damage with a walking track analysis using Sciatic Functional Index (SFI). However, SFI lacks resolving power for partial loss of nerve function. Local anesthetic injection can cause focal injury within the nerve to yield only a partial obstruction to nerve conduction. Specific tetanic force and muscle atrophy are more sensitive assays that will better assess functional damage. We expect muscle tetanic force to show impairment that correlates with the histologic damage observed in previous injection injury studies.

Conclusions: Nerve blocks are commonly performed for intraoperative pain control during surgical procedures and for alleviation of chronic pain. Injecting anesthetics into the nerve is a risk in this procedure, and there are reports of significant iatrogenic sequelae from nerve blocks. Despite these reports, literature is still being released claiming nerve injections do not cause injury. This study can contribute to the understanding that nerves should be treated with care and that all precautions should be taken to prevent the injection of anesthetics into nerve.

T35 NIH NHLBI Training Grant

016, 017 **Annor, Afua H**
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T35 NHLBI Training Grant
Summer Research Program
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Mentor: Corey R. Deeken, PhD
Effect of enzymatic degradation on the mechanical properties of biologic scaffold materials
Annor AH*; Tang ME*; Pui CL; Ebersole GC; Frisella MM; Matthews BD; Deeken CR
*These authors contributed equally to this work.
Introduction: Biologic scaffolds used in contaminated or chronic wounds must resist enzymatic degradation in order to support cellular attachment, deposition of new tissue, and angiogenesis. The goal of this study was to evaluate the effects of enzymatic degradation on the properties of biologic scaffold materials.
Methods: Nine materials were evaluated including porcine dermis, human dermis, bovine pericardium, and porcine small intestine submucosa-derived scaffolds. To establish the baseline "0 hour" properties prior to enzymatic exposure, ten (n = 10) specimens were hydrated in saline at 37°C and subjected to uniaxial tension at a rate of 300mm/min until failure. The other fifty (n = 50) specimens were incubated in a collagenase solution at 37°C for 2, 6, 12, 24 or 30 hours (n = 10 in each group), followed by uniaxial tensile testing.
Results: AlloMax, CollaMend, FlexHD, Permacol, Strattice, Veritas, and XenMatrix exhibited significantly reduced tensile strength after 30 hours of exposure to collagenase ($p < 0.01$ in all cases), but PeriGuard displayed a slight increase in tensile strength ($p = 0.0188$). Differences between crosslinked and non-crosslinked scaffolds of the same tissue type were also observed. For example, PeriGuard, a crosslinked bovine pericardium product, displayed greater strength than non-crosslinked Veritas throughout all exposure periods ($p<0.0001$ in all cases). Similarly, crosslinked porcine dermis (Permacol) displayed greater tensile strength than non-crosslinked Strattice and XenMatrix as well as crosslinked CollaMend throughout all exposure periods ($p<0.0001$ in all cases).
Conclusions: Biologic scaffold materials that rapidly deteriorate following in vitro exposure to enzymatic media may be at risk for similarly rapid degradation and loss of strength in the setting of contaminated wounds in vivo.

001 **Atkins, Jordan**
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Summer Research Program
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Mentor: Julie A. Margenthaler, MD
Assessment of imaging modalities in the prediction of response to neoadjuvant chemotherapy in patients with triple negative breast cancer
Atkins J; Cyr A; Appleton CM; Fisher CS; Margenthaler JA
Introduction: Triple negative breast cancer is a unique subtype of breast cancer that has been shown to be generally chemosensitive. We sought to investigate the accuracy of mammography (MMG), ultrasonography (US), and breast magnetic resonance imaging (MRI) in predicting the extent of breast residual disease in patients with triple negative breast cancer following neoadjuvant chemotherapy.
Methods: We performed a retrospective chart review and identified 153 patients with Stage II-III triple negative breast cancer who were treated with neoadjuvant chemotherapy between 2000-2010. Residual tumor size was estimated by MMG, US, and/or MRI following neoadjuvant chemotherapy but prior to definitive surgical intervention. The longest diameter of residual tumor measured with imaging was compared with the infiltrating residual tumor size at pathologic evaluation. Data were compared using Chi-square and $p<0.05$ was considered significant.
Results: Of 153 patients, thirty-one (20%) patients had a pathologic complete response (pCR); a pCR was suspected by imaging in 10 (33%), residual disease was suspected by imaging in 19 (61%), and imaging was not performed in 2 (6%). Of 122 (80%) patients with residual invasive disease on final pathology, 21 (17%) had MMG only, 8 (7%) had MRI only, 49 (40%) had MMG and US, 9 (7%) had MMG, US, and MRI, and 35 (29%) had no imaging. The imaging modality was accurate to within 1 cm of the final pathologic residual disease in 43 (35%) patients and within 2 cm in 70 (57%) patients. Accuracy was highest for US (57%) and MRI (53%), which were significantly more accurate than MMG (24%) ($p<0.05$).
Conclusions: Breast US and MRI were more accurate than mammography in predicting residual tumor size following neoadjuvant chemotherapy in patients with triple negative breast cancer. None of the imaging modalities were superior in predicting patients with a pCR. The relatively low accuracy of all three standard imaging modalities illustrates the need for alternative systems with improved sensitivity.

013 **Betti, Francesca**
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Mentors: Joshua Shimony, MD, PhD; Joel Garbow, PhD
Joint Estimation of AIF and perfusion parameters from dynamic susceptibility contrast MRI in mouse gliomas and comparison to tumor histopathology
Betti F; Chaffee K; Garbow J; Shimony J; Bretthorst L
Introduction: MRI perfusion measurements have been shown to correlate with angiogenesis and brain tumor progression and are a potential source of information about tumor development and response. However, traditional techniques of measuring brain perfusion parameters require an Arterial Input Function (AIF), which can be difficult to obtain in animal models. Here a local AIF (LAIF) model was used to determine brain perfusion parameters, a modification of the standard tracer kinetic model. Perfusion maps for each measurement were made and then compared to tumor histopathology and T1-weighted DSC images to determine the validity and utility of using perfusion parameters to quantify tumor extent.
Methods: DBT tumor cells were implanted into the brains of 20 female Balb/c mice. Mice were imaged on an 11.7T Varian scanner at various time points after the DBT cells were injected. The brain of each mouse was imaged with a multislice T2*-weighted spin-echo pulse and a T1-weighted spin-echo pulse sequence. For perfusion MRI, a series of T2*-weighted gradient echo fast low-angle shot images were acquired. The data were analyzed using the LAIF model. Image masks were generated for regions of elevated perfusion values and compared to histopathology and masks of contrast-enhanced regions of brain in T1W-postcontrast images.
Results: Using our LAIF model, the initial data show a better correlation between CBV, CBF, MTT and gamma values and tumor extent observed in histopathology than traditional T1W-postcontrast images. Masks made using composite information from CBV, CBF, MTT, and alpha also provide a better estimate of tumor histopathology than T1W images.
Conclusions: The LAIF model is showing itself to be a reliable function to determine perfusion parameters in rodent models, where traditional AIF models can be insufficient. Furthermore, a high correlation between perfusion parameters and tumor histopathology could represent a future utility of perfusion parameters to quantify tumors in conjunction with or instead of traditional T1W-postcontrast images.

117 **Broersma, Brittanie**
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The role of body morphology in the occurrence of driveline infections in LVAD patients
Broersma B; Judd A; Silvestry S
Introduction: Implantable left ventricular assist devices (LVADs) have improved outcomes for heart failure patients. Infections, particularly those of the driveline exit site, remain a major complication in patients supported by these devices. There is conflicting data regarding the correlation between obesity, as defined by BMI, and incidence of these infections. This study aims to examine morphologic factors including BMI, subcutaneous fat thickness at the exit site, and the length of driveline implanted in subcutaneous and muscle tissue to determine if there is any correlation with infection.
Methods: Retrospective chart review of all patients implanted with a HeartMate II LVAD at this institution was performed to identify patients as either having a driveline or pump-pocket infection or not. Fat thickness and driveline lengths were calculated from CT scans of patients that had available CT scan data.
Results: Patients with more of the driveline length implanted within the muscle have a lowered incidence of infection. Those with more length in the subcutaneous/fat tissue have a greater risk of infection.
Conclusions: The results of this study may suggest changes to be made in the implantation of LVAD drivelines to reduce the incidence of infection and improve outcomes in these patients.

097 **Charshafian, Stephanie**

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Stroke volume changes in ED patients with shock undergoing serial passive leg raising and fluid challenges

Charshafian S; Janssen A; Holthaus C; Fuller B; Williams K; Ablordeppey E; Wessman B; Theodoro D; Chang R; Williams J; Ahrens T; Hotchkiss R

Introduction: Stroke volume index changes with passive leg raising have been shown to predict volume responsiveness. The objective was to estimate the positive predictive value (PPV) of Passive Leg Raising (PLR) compared to 500ml saline boluses in ED patients with shock.

Methods: This is a subset analysis of adult ED patients prospectively randomized to fluid optimization (FO) in the ED between Aug 2010-Aug 2011 (ClinTrials ID: NCT01128413). The study is IRB approved with informed consent and being conducted at an academic ED with 90,000 visits/yr. Inclusion criteria are vasopressor use, or SBP ≤90 or MAP ≤65 after ≥20ml/kg IV fluids, or lactate ≥2.5 mmol/L. Exclusion criteria are pulse oximetry <90% or inability to do PLR. FO consists of non-invasive bioreactance monitoring of stroke volume (Cheetah NICOM®) and PLR testing. Patients deemed volume responsive (VR) receive a 500ml saline bolus if the PLR percent change (%Δ) in stroke volume index (SVI) or cardiac index is ≥15%. PLR is repeated immediately after each bolus with repeat boluses if ≥15%. If <15%, fluids are saline locked and PLR done every 30 minutes. SVI changes are calculated as: %ΔSVI=(Maximum challenge SVI-Average baseline SVI)/Average baseline SVI. Paired Students t-Test and descriptive analysis were performed (Microsoft® Excel).

Results: 7 patients (4 male) with a median age of 60 yrs (range 42-87) underwent 69 PLRs. 40 of 69 (58%) PLRs were VR and received fluid boluses. The median %ΔSVI are as follows: bolus 10% (IQR 1-22), PLR 32% (IQR 24-39). The PLR %ΔSVI was statistically different when compared to the bolus %ΔSVI ($p \leq 0.01$). The PPV of PLR %ΔSVI was 38%. 10/40 (25%) bolus events resulted in a negative bolus %ΔSVI.

Conclusions: In this small subset analysis, PLR SVI changes demonstrated suboptimal PPV when compared to fluid challenges. 25% of VR events predicted by PLR resulted in fluid administration that placed patients on the descending portion of the Starling curve, putting patients at risk for cardiogenic pulmonary edema. More study is needed, and when using PLR, quantitative incorporation of SVI or CI changes following fluid boluses may be needed to accurately determine VR.

127 **Chu, Jennifer**

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The impact of comorbidities and thumb osteoarthritis on patient rated hand function

Chu J; Adams A; Elfar J; Wong A; Calfee R

Introduction: Osteoarthritis (OA) of the thumb carpometacarpal (CMC) joint is one of the most common sites of arthritic degeneration seen by hand surgeons. With patient rated outcomes becoming central to orthopedic outcome research, this study will define the impact of thumb OA on patients' general health using validated health outcome instruments: the Short Form 36 (SF-36) and the Michigan Hand Questionnaire (MHQ). The effect of comorbidities on a hand-specific patient rated outcome measure (MHQ) will also be evaluated.

Methods: A joint prospective, case control study was conducted at Washington University and the University of Rochester. Forty-seven patients with thumb CMC OA and 147 controls over the age of 18 were enrolled. The subjects completed a demographic questionnaire, SF-36, MHQ, and relevant physical exams. Controls chosen for analysis were matched 1:1 with cases based on gender and age (+/- 5 years). The effect of comorbidity was determined by multivariate regression analysis for association with total MHQ score of the affected hand.

Results: Thumb OA results in poorer patient rated hand function and pain ratings compared to controls without a significant change in the aesthetic ratings of the hand. Univariate correlations with the MHQ total score in patients with thumb OA included age, gender, depression, upper extremity comorbidities, overall health, gender, and depression. Multivariate modeling showed that significant independent negative predictors in every subscale of MHQ scores were depression and upper extremity comorbidities (gender p=.06). The SF-36 query of overall health was the only predictor of total MHQ score in controls.

Conclusions: The results of this study suggest that patient rated hand function on the MHQ is affected by medical comorbidities and the effects change in the presence of thumb CMC OA compared to controls. Self reported depression and presence of upper extremity comorbidities are shown to have a significant negative impact on patient rated hand function in cases of thumb CMC OA. In the future, hand surgeons may be able to improve the reliability and performance characteristics of the MHQ by adjusting the score to account for such comorbidities.

007 **Cortez, Sarah**

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Why Wait: The effect of passive descent on length of second stage labor and maternal and neonatal outcomes.

Cortez S; Frey H; Odibo A; Macones G; Tuuli M; Shanks A; Roehl K; Cahill A

Introduction: Published evidence conflicts over the optimal management of second stage labor. We aimed to estimate the effect of passive descent, as compared to immediate pushing, on the length of second stage labor and risk of adverse birth outcomes.

Methods: This was a planned secondary analysis of a retrospective cohort study, designed to evaluate the predictive value of fetal heart monitoring, on all consecutive term (37 weeks or greater), singleton births from 2004-8. For this study, we compared women who used passive descent, defined as ≥30 minutes between completed dilation (10cm) and onset of pushing, to those who pushed immediately upon completion. Pregnancies of major fetal anomalies and those who did not reach the second stage of labor (time between completed dilation and infant delivery) were excluded, leaving 5,290 women available for analysis. Detailed data were collected on maternal characteristics, medical history, medications in labor, complete labor curves, and delivery, maternal, and neonatal outcomes. Bivariate and multiple logistic regression analyses were used to estimate the effect of passive descent on study outcomes while adjusting for potentially confounding effects.

Results: The passive descent group contained 1,054 (19.9%) of the women. The passive descent group's median total length of second stage labor was significantly longer (85 min) compared to the immediate pushing group's time (18 min, $p<0.01$). Median pushing time of the passive descent group was also longer (20 min vs. 10 min, $p<0.01$). Of the maternal outcomes assessed, passive descent differed from the immediate pushing group in rate of cesarean delivery (adjusted odds ratio 1.68, 95%CI 1.03-2.71), operative delivery (aOR 1.37, 95%CI 1.13-1.66) and postpartum hemorrhage (aOR 0.55, 95%CI 0.32-0.93). Of the neonatal outcomes assessed, passive descent differed from the immediate pushing group only in cord blood pH <7.2 (aOR 1.28, 95%CI 1.004-1.622).

Conclusions: Passive descent increased the time spent pushing as well as the length of total second stage labor. It was also associated with adverse outcomes including a greater risk of cesarean and abnormal umbilical cord pH.

070 **Fohtung, Bamvi Raymond**

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Pre-operative predictors and post-operative outcomes in laparoscopic converted to open ventral hernia repair

Fohtung B; Desai S; Costello KP; Frisella MM; Matthews BD

Introduction: Pre-operative parameters or other major perioperative complexities affect post-operative clinical outcomes of laparoscopic ventral hernia repair including complications such as pain, seroma, and recurrence, as well as the incidence of conversion from laparoscopic repair to an open procedure. Conversion results in longer operative time and increased operative stress for the patient. In this study, we investigated the pre-operative predictors and post-operative outcomes for patients who had a laparoscopic converted to open ventral hernia repair. The effect of a suprapubic hernia, a pre-operative factor not invested before, was also investigated in terms of outcomes in laparoscopic ventral hernia repair.

Methods: After IRB approval, medical records were reviewed for patients who had previously undergone a laparoscopic ventral hernia repair. Patient demographic information and other co-morbidities including age, sex, BMI, length of hospital stay, number of previous abdominal surgeries, number of previous hernia repairs and size of the hernia defect, ASA classification, prednisone or other immunosuppressant use, tobacco use, airway disease, diabetes and cancer were collected. Measures of operative complexity were also investigated including time of access into the abdomen, time of adhesiolysis, time of mesh placement, and total operative time.

Results: A total of 357 subjects were enrolled in this study. Data is given as mean ± standard deviation. The study included 154 men and 203 women with an average age of 55±12 years and an average body mass index (BMI) of 34.0±7.8. Of these patients, 11 (3%) were converted from a laparoscopic to an open procedure and 85 (24%) had hernias in a suprapubic location. With respect to outcomes, 16 (5%) had recurrences, 114 (32%) complained of pain during their first post-operative visit and 71(20%) had a seroma during their first post-operative visit.

Conclusions: Understanding the factors that predict conversion to open repair would help surgeons select patients eligible for a laparoscopic repair.

055 **Ganju, Akshay**

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Knowledge and recommendations on tobacco cessation and other preventive interventions among internal medicine staff in Guatemala teaching hospitals

Ganju A; Corral JE; Barnoya J

Introduction: Guatemala is currently undergoing an epidemiologic transition. Preventive interventions are key to reducing the burden of chronic diseases, and smoking counseling and cessation are among the most cost-effective. Internal medicine staff members are fundamental to providing these interventions and their knowledge and practices are a cornerstone of chronic disease control. To his study evaluates the knowledge of chronic disease prevention interventions and current recommendations on screening for chronic diseases among Guatemalan internal medicine staff.

Methods: A validated survey was used to assess knowledge of current recommendations on screening for chronic diseases (A and B recommendations according to the US Preventive Services Task Force). Trained research assistants interviewed 387 interns, residents, staff and medical directors in the Internal Medicine departments of every teaching hospital in Guatemala.

Results: While data analysis is still ongoing, preliminary results show that there are gaps in knowledge amongst Internal Medicine staff. For example, doctors often prioritize non-cost effective interventions (EKGs for heart disease, for example) over proven interventions (screening for colon cancer, for example). Physicians also will often pick less effective screening methods (fecal occult blood testing instead of colonoscopies for colon cancer, for example).

Conclusions: We hypothesized that Guatemalan internal medicine staff are inadequately trained in preventive medicine. Our data should prove useful to strengthen preventive medicine education and implement a much needed cost-effective, evidence-based screening program. Such changes are vital in low-income countries where access to medical treatment is limited.

115 **Henke, Lauren**

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Clinical and clinicopathological outcomes of papillary thyroid carcinoma in relation to the presence of the BRAF V600E mutation

Henke L; Grigsby P

Introduction: According to the American Cancer Society, approximately 40,000 people will be diagnosed with well-differentiated thyroid cancer in the United States in 2011. This compares to approximately 13,000 diagnosed in 1995. Without doubt, the prevalence of this cancer is significantly increasing. Currently, therapy guidelines do not take into account the presence of the BRAF V600E mutation. On a cellular level, V600E mutations are associated with unchecked proliferation, transformation, tumorigenicity, and suppressed apoptosis. The purpose of this study is to evaluate the relationship between clinical and clinincopathological outcomes of PTC and the BRAF V600E mutation. Although the study is ongoing, it is predicted that this research will identify this mutation as a prognostic factor that will guide therapy for patients with thyroid cancer such that aggressive therapy can be administered to those at high risk for negative outcomes from their cancer and that therapy can be minimized for those who are at low risk for developing recurrent disease.

Methods: Formalin-fixed, paraffin-embedded (FFPE) tumors of 629 patients with papillary carcinoma of the thyroid were tested for the *BRAF* V600E mutation over the period of one year. Presence/absence of the mutation was evaluated by restriction length polymorphism analysis (RFLP). Specifically, polymerase chain reaction (PCR) was followed by digestion with the restriction enzyme TspRI and resolved by gel electrophoresis. Statistical analysis to compare patients' clinical outcomes with their tumor statuses was performed using SAS Statistical Software. Comparisons of groups were executed using standard statistical analysis, logistic regression, and Cox multivariate logistic regression. Comparisons of survival estimates were completed using the Kaplan-Meier Method and equivalence of survival was tested with the Wilcoxon Log-Rank Method.

Results: It is anticipated that there will be a correlation between the presence of the BRAF V600E mutation and clinicopathologic features that are known to be associated with poor prognostic outcomes. It is not known if BRAF V600E is an independent prognostic factor.

Conclusions: Although the study is ongoing, it is predicted that this research will identify this mutation as a prognostic factor that will guide therapy for patients with thyroid cancer such that aggressive therapy can be administered to those at high risk for death from their cancer and that therapy can be minimized for those who are at low risk for developing recurrent disease.

015 **Hong, Charles R**
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***In vivo* optical imaging of antibodies to radiation inducible antigens on tumors**

Hong C; Hallahan D

Introduction: The enhanced permeability and retention (EPR) effect describes a phenomenon where nanoparticle sized material tends to accumulate in tumors at an increased level compared to normal tissue. This allows passive targeting of nanomaterial to tumors. In our laboratory, we have developed a series of antibodies and peptides to GRP78 and TIP-1 surface receptors that enable specific targeting of cancer cells after exposure to radiation. These molecules have been used to actively target nanoparticles to cancer in previous *in vivo* studies. The aim of this study is to develop a method to account for the passive and active components of targeting using nanoparticle sized materials *in vivo* through the use of optical imaging methods. This method will allow for comparison of two actively targeted nanoparticles *in vivo*, while also accounting for passive targeting of the nanoparticle due to the EPR effect.

Methods: A549 human lung carcinoma tumors were initiated in athymic nude mice in the hind limbs bilaterally. The left-sided tumors were treated with 3 Gy XRT twice while the right-sided tumors were given sham radiation. The mice received dual-probe injections of both antibody targeted and nontargeted IR dyes or two different antibody targeted IR dyes. Mouse monoclonal antibodies against GRP78 (2D6F9) and TIP-1 (2C6F3) were compared with a nonspecific agent (mouse IgG2b) or each other.

Results: In preliminary studies, antibody targeted probes exhibited greater cancer specific binding compared to nontargeted probes. Higher binding with the GRP78 antibody was observed compared to the TIP-1 antibody. No differences were observed between irradiated and non-irradiated tumors.

Conclusions: The study suggests that mouse monoclonal antibodies against GRP78 and TIP-1 are promising agents for cancer targeted therapy or imaging. However, selectivity for irradiated tumors was not observed. Further studies with other tumor cell lines or alternate administrations of irradiation to localize treatment to one tumor are warranted.

No Poster Displayed

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Feasibility study of education interventions for emergency COPD patients

Lewis LM; Jorif M; Dwyer E

Introduction: Chronic obstructive pulmonary disease (COPD) is the fourth most common fatal disease in the United States. It develops as a result of narrowing of airways and permanent distension of lung alveoli which consequently leads to a decrease in air conduction. Education is an important component of managing COPD. The Global Initiative for Chronic Obstructive Lung Disease states that "patient education can help improve skills, ability to cope with illness, and health status." We believe that providing health literacy appropriate educational interventions to patients with COPD will increase their knowledge of their disease and improve self management. Our long term goal is to develop and implement a health education program that can be offered to emergency patients with COPD. We had several objectives: Determine if attending an educational seminar improves understanding of management of COPD and lifestyle/behavioral changes. Determine if a modest financial incentive will improve attendance at a COPD educational seminar. Compare health outcomes (mean number of ED visits, hospitalization days, missed days at work) between the intervention and control groups. Participants: 18-70 years' old ED COPD patients ($FEV_1 \leq 70\%$)

Methods: This would be a randomized controlled interventional study. ED patients with an exacerbation of their COPD, once stabilized, will be eligible. Consenting subjects will undergo literacy tests, and complete questionnaires regarding COPD knowledge and self-management skills. Subjects will be randomized to 1 of 3 groups: (1) usual discharge instructions (control group); (2) usual discharge instructions and assignment to a 1 hour educational intervention; (3) usual discharge instructions and assignment to a 1 hour educational intervention with a $20 incentive to attend. All groups will be followed up at 1 month by telephone to determine knowledge and self management of their disease. They will also be asked general health questions regarding their COPD.

Results: Knowledge and self-management scores will be compared between groups using ANOVA. The mean number of days of work or school missed due to COPD exacerbation will be compared between groups using 95% confidence intervals. Limitations included: Psychological distress of subjects, problems with travelling to intervention, issues with patients participating in follow up protocol.

Conclusions: Results are in progress.

119 **Judd, Andrew W**

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Effect of anticoagulation status on stroke in patients with continuous flow implantable left ventricular assist devices

Judd AW; Broersma B; Silvestry SC

Introduction: Cardiac transplantation is the definitive therapy for refractory congestive heart failure. However, the supply of donor hearts remains flat while demand increases. To address this demand the use of left ventricular assist devices has continued to grow both as a bridge to transplant and as a destination therapy in transplant-ineligible patients. These devices carry significant health risks including risk of stroke from thrombus formation, necessitating anticoagulation therapy – however anticoagulation therapy itself carries increased risk of bleeding and hemorrhagic stroke. The purpose of this study is to examine stroke event rates and anticoagulation levels in LVAD patients and determine the appropriate ranges for optimal risk reduction for both stroke and bleeding events.

Methods: Data from 252 LVAD recipients at Barnes-Jewish Hospital was reviewed and the number of stroke events was recorded. Each patient's data was recorded from date of device implantation to successful transplantation, death, or the present day if neither outcome had been reached. Additional risk data was recorded for each patient including demographic stroke risk factors, CHADS2 score and presence of LVAD site infections. INR values surrounding each stroke or bleeding event were recorded.

Results: Of the study patients, 99 have been transplanted, 97 have died, and 90 are currently alive with LVAD in place. 24 patients died after heart transplantation. Stroke events occurred in 17.6% of patients and serious infection occurred in 19.8%. Additional work with the data is ongoing. We anticipate finding a correlation between measured INR at the time of event and the event's etiology (hemorrhagic vs. ischemic stroke). Additionally we anticipate a statistically significant difference between average INR values in patients who experienced stroke and patients who were free of stroke.

Conclusions: If the results of this study are as anticipated they will represent a base of clinical knowledge from which an optimal anticoagulation regimen can be determined for patients on LVAD support, and potentially act as the basis for a randomized controlled trial.

060 **Juengel, Braden N**

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CDR 0.5/uncertain as a distinct diagnostic group

Juengel B; Roe CM; Storandt M; Morris JC

Introduction: The Clinical Dementia Rating (CDR) is a diagnostic tool for measuring the severity of dementia. The CDR is based on a clinical interview with the participant and an informant, independent of neuropsychological test results. A CDR of 0.5 is a broad classification for "very mild dementia" that we subdivide into 0.5/DAT, which represents early effects of incipient Alzheimer's Disease, and 0.5/uncertain, in which impairment due to DAT cannot be conclusively diagnosed.

Methods: Three groups of participants from the Knight ADRC enrolled after 2001 were studied: CDR 0 controls (N=130), CDR 0.5/uncertain (N=77), and CDR 0.5/DAT (N=190). Scores on a neuropsychological battery testing episodic memory, semantic memory, working memory, and visuospatial skills were compared using analysis of covariance, adjusted for age and education, followed by post-hoc analysis. Amyloid beta-42 was collected in cerebrospinal fluid by lumbar puncture, and PET imaging was done with Pittsburgh Compound B and a Mean Cortical Binding Potential (MCBP) was calculated.

Results: All cognitive measures except Digit Span Forward and Digit Span Backward differed significantly across the three groups. CDR 0.5 uncertain was not significantly different from CDR 0 normal controls in: Information, Mental Control, Digit Span Forward, Digit Span Backward, Letter Fluency, and the Working Memory composite. CDR 0.5 uncertain was not significantly different from CDR 0.5 DAT in: age, education, and Digit Span Backward. CDR 0 and CDR 0.5 DAT were significantly different in all variables measured.

Conclusions: CDR 0.5/uncertain appears to exists distinctly between CDR 0 and CDR 0.5/DAT in degree of impairment in nearly all domains. Once more individuals with longer follow-up periods are available, the CDR 0.5/uncertain group should be studied further, including longitudinal analysis to examine if underlying pathology, as indicated by biomarkers, can predict future clinical and cognitive decline.

122 **Jupitz, Jennifer**
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Mentors: Michael P. Kelly, MD; Lawrence G. Lenke, MD
Assessment of outcomes following revision surgery in pediatric spinal deformity patients
Jupitz JM; Kelly MP; Lenke LG
Introduction: An estimated 10% of pediatric patients who undergo surgery for spinal deformity will require revision surgery. No large study investigating the outcomes of revision pediatric spinal deformity surgeries exists. The primary goal of this study is to determine the rate of and reason for repeat revision, spinal deformity surgery at a single institution.
Methods: Patient charts and operative reports were reviewed from pediatric patients who underwent revision surgery for spinal deformity at this institution. Demographic variables including diagnosis, comorbidities, reason for revision, age at revision, body mass index, ASA score and incidence of smoking were recorded. Previous surgery and any prior infections were also noted. Details of the revision procedure were recorded, including anterior/posterior, levels fused, use of osteotomies, surgical approach, instrumentation, bone graft, and BMP. Estimated blood loss, case length, and complications were recorded. For those patients who later received additional surgeries, the number of repeat revisions was recorded. Pre- and post-operative Scoliosis Research Society – 22/24 scores will be compared. The overall rate of repeat revision will be calculated. Changes in SRS scores will be determined, as well as potential risk factors for repeat revision surgery.
Results: Risk factors associated with poorer outcomes following pediatric spine surgery include the use of corrective osteotomies, implant use, and a diagnosis of neuromuscular scoliosis. Additionally, there is evidence for an increased incidence of infections and new neurologic deficits with revision surgeries versus index procedures. This study will identify the risk factors specifically associated with poorer outcomes, and will quantify a repeat revision rate for the pediatric population.
Conclusions: An accurate portrayal of the risks and benefits of revision surgery will help patients and physicians to make informed decisions regarding repeat revision surgery, and to form realistic expectations of results following the procedure. The results will also guide efforts to improve outcomes and modify potential risk factors for repeat revision surgery.

072 **Laurido-Soto, Osvaldo J**
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Mentors: Daniel A. Hunter, RA; Philip Johnson, PhD; Susan E. Mackinnon, MD
Evaluation of nerve injection injury with 3 common anesthetics using quantitative histomorphometry
Laurido-Soto OJ; Bery A; Zieske L; Hunter DA; Johnson P; Mackinnon SE
Introduction: Intraneural administration of local anesthetics has been associated with nerve damage. In the recent years there has been a paradigm shift in the field of Anesthesiology stating that injecting local anesthetics into nerves is not harmful, this might led to iatrogenic injuries. The purpose of this study is to evaluate the effect off injecting different commonly used local anesthetics into different levels of the nerve.
Methods: Lewis rats will be randomly distributed into 2 different treatment groups: intrafascicular or extrafascicular injection of 8 microliters. At a 2 week endpoint animals will be sacrificed, and the sciatic nerve at the injection site will be evaluated with light microscopy and quantitative histomorphometry.
Results: The injection of the various compounds will have different effects on the histomorphometry of the injured nerve. Injection of 0.9% Saline leads to no nerve damage regardless of positioning, while the injection of 10% Phenol leads to nerve ablation regardless of positioning. The injected anesthetics will show that with intrafascicular placement: 1% Lidocaine and 0.5% Ropivicaine produces moderate damage while Bupivicaine will show mild damage. The results should show that while intrafascicular injection causes nerve damage extrafascicular injection causes negligible damage. Unfortunately, because we used 8 microliters instead of 50 microliters, this amount of injectate seemed too small to cause any considerable amount of damage.
Conclusions: Damage to peripheral nerves from intraneural injection with local anesthetic could lead to neuropathic pain and/or functional loss that would affect both the productivity and psychosocial status of the patient. By doing this study, a set of guidelines based on the rat model, can be created to educate anesthesiologists on the effects of injecting local anesthetics into nerves, thereby reducing the number of nerve injuries and unnecessary patient morbidity. Emphasizing that extraneural placement is mostly safe while intraneural injection should be avoided.

051 **Letvin, Adam**

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Inducing delayed reproductive senescence with small molecules

Letvin AN; Kornfeld S

Introduction: The relationship between reproductive and somatic aging is poorly understood. Many factors have been identified that can delay senescence in a number of model organisms, but the effects of these interventions on the reproductive degeneration that proceeds senescence has been largely unexplored. The small molecules Imipramine, Yohimbine and Captopril have recently been implicated in delayed senescence in *C. elegans*. This study observed the effects of these drugs on progeny production in *C. elegans* in order to determine whether or not reproductive aging is controlled by similar pathways.

Methods: As opposed to the self-fertile hermaphrodites, mated hermaphrodites are no longer sperm limited, making progeny production an accurate predictor of reproductive senescence. L4 stage hermaphrodites were mated on drug-infused plates with adult males for a specified period of time. The hermaphrodite was then transferred to a new drug-infused plate every 24 hours for the duration of the worm's reproductive life. Progeny were counted approximately 48 hours after the transfer of the mated hermaphrodite.

Results: Mating was suppressed and suicidal or matricidal tendencies appeared to be more pronounced in the treated populations. Across all trials, progeny production rises sharply after day 1, peaks on day 2 or 3 with an average of around 200 progeny per day, and then enters into a sharp reproductive decline after day 4. In the control trials, the *C. elegans* progeny production stopped altogether by day 10. In the Imipramine trials, progeny production by day 7 or 8 was noticeably higher than that of the controls, and did not stop progeny production until day 12. Captopril-treated C. elegans enter into a rapid reproductive decline that mirrors expression of the sickly phenotype. Yohimbine-treated *C. elegans* show erratic, although sometimes extensively delayed reproductive decline.

Conclusions: It is possible that suppressed mating rates reflect neurological changes, and increased suicidal or matricidal tendencies reflect increased stresses in the treated populations. While Captopril does not appear to delay reproductive senescence, more assays will have to be run to determine whether or not the results from the Imipramine and Yohimbine trials are reproducible or significant.

124 **McAllister, Jared**

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Clinical importance of nucleolin in pediatric astrocytoma patients

McAllister J; Haydon D; Leonard J

Introduction: Gliomas make up approximately 40% of the brain tumors in the pediatric population. The prognosis for high-grade glioma patients is poor; only rare patients survive beyond two years after diagnosis. We believe that nucleolin is a critical regulator of glioma cell growth and that its knockdown could allow glioma control. Nucleolin expression is known to be high in many cancer cells, but the expression of nucleolin in gliomas has not been previously reported. Nucleolin presents a possible avenue of treatment for glioma patients because it can be targeted by synthetic peptides. The purpose of this study is to determine whether nucleolin expression in pediatric astrocytomas correlates with overall survival or predicts the likelihood of disease progression.

Methods: We have identified patients diagnosed with pediatric astrocytomas in the CDI Brain Tumor Bank at Children's Hospital and have extracted relevant clinical information. Tumor samples from each patient will be graded by an independent neuropathologist, put into a tissue microarray, and stained for nucleolin expression. The level of nucleolin expression will then be correlated with the primary outcomes of overall survival and time to disease progression.

Results: We anticipate that increased nucleolin expression will correlate with worse overall survival. In patients with pilocytic astrocytomas, we anticipate that increased nucleolin expression will correlate with a greater likelihood of disease progression.

Conclusions: Confirmation of the correlation between nucleolin expression and prognosis will allow nucleolin expression level to act as a new prognostic indicator for the management of pediatric glioma. This will also allow us to proceed with further exploration into nuceolin knockdown using synthetic peptides that bind nucleolin as a novel treatment for pediatric gliomas.

052 **Prendergast, Niall**

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Mentor: Timothy Graubert, MD

Regulatory effects of caspase-9 knockdown on a gene set Identified in AML-susceptible mouse strains

Prendergast NT; Graubert TA

Introduction: Therapy-related acute myeloid leukemia (t-AML) is a hematologic malignancy with poor prognosis which is associated with exposure to alkylating chemotherapy. Cahan and Graubert (2010, BMC Genomics) identified 30 gene networks whose pre-exposure transcriptional state predicted AML susceptibility in mice. Caspase-9, the gene encoding for the primary initiator caspase of the intrinsic apoptotic cascade, is believed to regulate one such network. The purpose of this work was to develop a protocol for siRNA knockdown of caspase-9 in primary bone marrow cells, and to then determine the regulatory changes in the gene network.

Methods: Primary bone marrow cells were harvested from C57/B6 mice and transfected with siRNA using Dharmacon's proprietary Accell protocol and reagents in order to identify the most efficacious siRNA construct; knockdowns were assessed by Western blot. Stem and progenitor (kit+/lin-) cells were then harvested from C57/B6 mice and transfected with the identified RNA. RNA was extracted after 48 hours, and qRT-PCR is to be done to assay transcriptional changes.

Results: One siRNA was identified as being the most effective, and a protocol for transfection of primary bone marrow cells was achieved. The resulting system was used to transfect two biological replicates of kit+/lin- (stem and progenitor) cells. These cells were harvested after 48 hours and RNA was extracted. Further data collection and analysis is ongoing.

Conclusions: At this time, the most valuable product of this work is the transfection protocol for short-term siRNA knockdown in primary bone marrow cells, which has been difficult at best. RNA analysis is ongoing, and the hope is that that analysis will yield predictive information regarding AML susceptibility. This could lead to the tailoring of chemotherapeutic regimens in the future, so as to minimize the risk of t-AML to susceptible individuals.

009 **Rose, Alexander B**

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Pattern ERG as an indicator of RGC loss in mouse glaucoma models

Rose AB; Lukasiewicz P

Introduction: The pattern electroretinogram (ERG) can be used to cancel out linear signals (a & b waves) and expose the underlying non-linear signals (notably P1 & N2). These non-linear signals depend upon retinal ganglion cell (RGC) functionality and have been shown to be reduced or eliminated in mammals with optic nerve crushes (ONC), optic nerve transections, and glaucoma, all of which cause RGC degeneration. Pattern ERGs are usually recorded externally at the cornea as a change in voltage in response to reversing the contrast of a grating or checkerboard pattern. While previous studies have generally been performed on intact mice, our study hopes for the ability to perfuse drugs and less signal noise by recording at the level of the eye cup. We aim to investigate whether functional RGC loss, as recorded by the pattern ERG, correlates with cytoarchitectural loss.

Methods: ONCs were performed in one eye of wild-type mice while the other eye was not crushed for comparison and control of variability between mice. The length of time post-ONC varied from 1-5 days. Dissections were performed under infrared lighting with only dim background light. The light stimulus came from an OLED flashing a grating of approximately 0.5 cy/deg at 1 Hz.

Results: Much effort went into developing an apparatus and protocol that could reliably and consistently measure pattern ERG signaling with minimal noise and thus minimal need for signal averaging (1-2 orders of magnitude less than intact animal studies). Preliminary data showed a decrease in pattern ERG signaling in ONC eyes, relative to the normal eye. There was also a corresponding decrease RGC count in ONC eyes relative to the normal eye.

Conclusions: The preliminary results of this study suggest that functional RGC loss does indeed correlate with cytoarchitectural loss. Our current research direction is to collect more data using our now proven research apparatus and protocol in order to quantify the nature of the correlation between functional RGC loss and cytoarchitectural loss. Our future research direction with clinical application is to investigate whether pattern ERG can be used as a more sensitive test to positively identify patients with early stage glaucoma prior to the presentation of visual field deficits.

062 **Rubins, David M**

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Comparison of CSF lab values and functional connectivity as biomarkers for Alzheimer's disease

Rubins DM; Ances BM; Brier M; D'Angelo G; Fagan AM; Benzinger TL; Holtzman DM; Morris JC

Introduction: Alzheimer's disease is the most common form of dementia and the number of people affected is expected to double over the next 20 years. It is thought that the neural changes in the disease are present well in advance of the clinical manifestations, and if they could be detected, more effective therapeutic approaches could be developed. We examined the ability of two categories of biomarkers, CSF lab values and functional connectivity, in discriminating between subjects with and without clinical dementia.

Methods: To look at the discriminatory abilities of the biomarkers, we used five different classification methods that provided a mixture of linear and non-linear separators that are well-represented in the literature. We then used CSF lab values (aβ42 and tau protein levels) and functional connectivity (FC) metrics from 321 subjects as inputs to the classifiers and Clinical Dementia Rating (CDR) status as the output. We derived a ROC curve for each classifier and each set of feature inputs and calculated its Area-Under-the-Curve to compare between the different methods. Additionally, to see how well FC metrics could predict pathology, as opposed to clinical manifestation, we also ran classifications with FC metrics as inputs and presence of pathological lab values as outputs.

Results: The most effective classifications came from the Linear Discriminant Analysis classifier. All of the CSF lab values outperformed the FC metrics in classifying subjects, and the ratio of tau protein to aβ42 was the most predictive. Additionally, combining FC metrics with CSF lab values was no more predictive than CSF values alone. FC metrics were better at predicting abnormal lab values than CDR, and were better at predicting abnormal tau protein levels than abnormal aβ42 levels.

Conclusions: Currently, CSF lab values are more predictive measures of CDR status than FC metrics. However, obtaining lab values is an invasive procedure, so future research should be focused on improving FC predictive ability. Additionally, these biomarkers should be reevaluated in longitudinal studies to truly understand their predictive potential.

042 **Salman, Rabia**

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Mentor: Milan Anadkat, MD

Clinical characteristics predictive of superinfection in patients with EGFR-inhibitor associated eruptions

Salman R; Anadkat MJ

Introduction: Many recently developed chemotherapeutic agents involve inhibition of the epidermal growth factor receptor (EGFR). EGFR activation results in cellular growth, proliferation, and angiogenesis. EGFR inhibitors (EGFRIs) are thus effective at curtailing the growth and proliferation of certain cancers, but often result in unwanted dermatological side effects, most notably painful, itchy or disfiguring rashes. Oncologists are often forced to discontinue treating patients with EGFRIs because of skin toxicities. The Cutaneous ChemoTherapy REACTion (CCT REACT) database is an ongoing retrospective and prospective analysis of all dermatology patients with skin reactions to any form of chemotherapy. Currently, the majority of patients enrolled have received EGFRIs. Multiple data points are followed, including demographics, characteristics of skin toxicities, response to treatment, and concomitant therapy. This database allows us to assess management and to examine characteristics that may aid in predicting complications such as superinfection of EGFRI associated eruptions.

Methods: This study involved a retrospective review of the CCT-REACT database. In order to specifically examine the characteristics that might predict superinfection of EGFRI associated papulopustular eruptions, we assessed patient demographic data, clinical characteristics from photos and records, culture results, location of the rash, and concomitant therapies to see how these factors alter patient risk profiles.

Results: We anticipate that certain clinical characteristics will predict the presence or absence of skin infection in patients with EGFRI associated rashes. For example, we predict that location over the extremities, atypical for the EGFR eruption, will be most commonly associated with superinfection.

Conclusions: EGFRIs have recently been the focus of much attention due to their potential as anti-neoplastic agents. However, treatment with EGFRIs must often be discontinued due to the severity of side effects. By better predicting which patients may experience complications and adjusting our management accordingly, we may be able to keep patients on these potentially life-saving therapies for prolonged periods.

024 **Skala, Stephanie**

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Mentors: Gina M. Secura, PhD, MPH; Jeffrey F. Peipert, MD, PhD

Annual STI screening among young women enrolled in the Contraceptive CHOICE Project

Skala SL; Secura GM; Peipert JF

Introduction: Although the Centers for Disease Control and Prevention recommends annual chlamydia screening for women ages 25 years and younger, current screening rates in the US remain low. The Contraceptive CHOICE Project offers annual sexually transmitted infection (STI) screening to all study participants at no cost using home or clinic-based testing. Our objective was to determine predictors of completion of annual STI screening among sexually active young women.

Methods: We analyzed survey data from 2,607 sexually active women 25 and younger including demographic characteristics, sexual risk behaviors, relationship characteristics, and contraceptive method use. We considered receipt of a completed test kit within 56 days of the annual survey a completed screen. A multivariable model to predict screening completion was created using Poisson regression with robust error variance and included factors significant in univariate analyses.

Results: Sexually transmitted infection screening at 12-month follow-up was completed by 57% (n=2,425) of women. Screening completion was most strongly associated with a college education or higher (RR_{adj}=1.2, 95% CI: 1.1, 1.3) and use of home testing (RR_{adj}=1.3, 95% CI: 1.2, 1.5). Women who reported new sexual partners in the past year were 10% more likely to complete screening (RR_{adj}=1.1, 95% CI: 1.0, 1.2).

Conclusions: Many sexually active young women fail to adhere to screening recommendations for sexually transmitted infection. Removal of financial barriers and easier access increased rates of screening; yet additional barriers remain. A first step toward more effective strategies for increasing annual screening rates is to increase the availability of home testing kits.

027 **Steinhorn, Rachel**

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The impact of morphine exposure in the preterm infant on brain development in childhood

Steinhorn RH; Zhang Y; Inder TE

Introduction: Analgesics such as morphine and fentanyl are often used in the Neonatal Intensive Care Unit (NICU) to ameliorate the neonatal experience of pain, which may have deleterious effects on anxiety, depression, and nociception later in life. The premature brain is particularly susceptible to the detrimental effects of pain, but there is limited information about the long-term neurological and cognitive sequelae of the analgesics most commonly used to treat it in the NICU. Preliminary results suggest that fentanyl is associated with cerebellar hemorrhage, reduced cerebellar and frontal lobe growth, and impaired gyrification. The present study examines the impact of receiving morphine as a premature neonate on clinical outcome and brain development at seven years of age.

Methods: 15 seven-year-old subjects who were born prematurely and received morphine in the NICU were compared with matched controls. Hemispheric pial surface area, gray matter volume, white matter volume, and cortical thickness were calculated from magnetic resonance imaging (MRI) scans analyzed in Freesurfer v4.4. Clinical characteristics, MRI volumetrics, and performance on cognitive tests were compared between groups.

Results: Children who received morphine as premature neonates showed no statistically significant neurological or clinical differences compared to children who had not received morphine in the NICU. Scores on the BSID-ii mental and psychomotor developmental indices and the ITSEA competence subtest showed no significant difference between groups, though the morphine group did perform worse on the delayed alternation test of executive function. There was no dose-dependent effect of morphine.

Conclusions: Exposure to boluses and low-level infusions of morphine in the NICU is not associated with changes in clinical outcome, brain metrics, or cognition. The findings suggest that morphine may result in better long-term neurological outcomes than other analgesic agents commonly used in the NICU, such as fentanyl. Further research into morphine's impact on brain gyrification and potentially vulnerable regions involved in executive function is warranted.

003 **Steinmetz, Allison**

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Functionalizing RNA helicases mutated in estrogen receptor positive breast cancer

Steinmetz A; Weber J

Introduction: Among all cancers, breast cancer is the second leading cause of death in women, affecting over 200,000 people a year in the United States and almost a million women worldwide. Whole Genome Sequencing (WGS) studies in breast cancer patients reveal numerous mutations, insertions, deletions, inversions and translocations. However, WGS does not identify which of the mutations are important to onset, evolution, or pathology. In the WGS performed on 50 Estrogen Receptor positive (ER+) patients at Washington University School of Medicine, few genes were mutated 3 or more times. One such gene was eukaryotic translation initiation factor 4 gamma 3 (eIF4G3). This gene, with other RNA helicases and RNA helicase interacting proteins mutated in the cohort, make up an RNA helicase network. Our goal is to functionalize the RNA helicase network of proteins mutated in ER+ invasive breast cancer genomes.

Methods: Using non-tumorigenic human mammary epithelial cells (HMECs), primary mouse mammary epithelial cells (MMECs), and ER+ breast cancer cell lines, we are investigating the role of the RNA helicase network members in growth and proliferation. HMECs, MMECs, and select ER+ breast cancer cell lines were infected with lentivirus encoding shRNAs to down-regulate endogenous protein levels. We are cloning overexpression plasmids into a lentiviral backbone to infect into the same cell lines. The role of the RNA helicase network members in transformation will be assessed using oncogenic RasV12 mutant transformed *Arf*-deficient MMECs. We will infect these cells with lentivirus expressing shRNA against helicase proteins to determine if down-regulation of endogenous protein levels prevents cellular transformation by soft agar assays.

Results: Preliminary experiments demonstrate that loss of eIF4G3 promotes proliferation, while loss of DHX9 halts cell division revealing that the RNA helicase network proteins mutated in ER+ breast cancer includes both positive and negative regulators of proliferation.

Conclusions: This project is still in progress, but we expect that the RNA helicase network members will affect cell growth and proliferation, cell death, anchorage-independent growth, ribosome biogenesis, and mRNA translation levels.

059 **Thomas, Stephanie**

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Notch2 signaling regulates the development of a distinct subset of CD24$^-$ dendritic cells

Thomas SR; Satpathy A; KC W; Albring JC; Turkoz M; Murphy TL; Kopan R; Murphy KM

Introduction: Dendritic cells (DCs) are professional antigen-presenting cells in the mammalian immune system. They capture, process, and present antigens to naïve T cells, initiating an adaptive immune response. While many subsets of DCs have been identified, and a variety of functions and developmental programs have been discovered, not all subsets and features of DCs have been fully investigated. This research explores a previously unstudied subset of DCs, characterizing its surface markers, its location within lymphoid tissues, and its developmental pathway.

Methods: Multiparameter flow cytometry, epifluorescent microscopy, and DNA microarrays were used to characterize DCs isolated from wild type mice and from genetically-modified mice missing certain transcription factors or signaling proteins.

Results: We identified two distinct populations of CD24$^-$ DCs, one that is CD11b^{hi} ESAM$^-$, and one that is CD11b^{int} ESAM$^+$. The ESAM$^+$ DCs are found in the spleen but not in skin-draining lymph nodes, whereas the ESAM$^-$ DCs are found in both locations. ESAM$^+$ DCs are absent in mice that are missing Notch2 from hematopoietic cells, but ESAM$^-$ DCs appear unaffected, indicating that Notch2 signaling is required only for ESAM$^+$ DC development. Both populations were found to arise from pre-cDCs and require Flt3L signaling for their development. Microarrays analysis shows that these two subsets are very similar in their gene expression, but their key differences may illuminate possible different roles or homing processes.

Conclusions: This research shows that two distinct subsets exist within the CD24$^-$ DC subset, and that these two subsets have different developmental requirements. While the two subsets do not show drastic differences in gene expression, their divergent development suggests that they may serve slightly different roles within the immune system. Further study using epifluorescent microscopy and infection models will help identify the role of these newly identified ESAM$^+$ DCs. Future findings may even impact the interpretation of prior DC function studies, which treated the CD24$^-$ DCs as a homogenous population.

090 **Wong, Kristine**
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Mentor: Timothy Hullar, MD
Recalibration of auditory-vestibular simultaneity
Wong K; Hullar T
Introduction: Multisensory integration is important for accurate perception of the world around us. This integration includes the temporal association of two different stimuli. It will be important to determine whether the neural circuitry responsible for this type of sensory processing is flexible. The purpose of this study is to assess the adaptability of the temporal integration of vestibular and auditory stimuli.
Methods: Subjects will judge whether vestibular and auditory stimuli are simultaneous. The stimuli consist of an oscillating rotational chair (i.e. the subject is seated while moving back and forth in the horizontal plane) and a constant auditory stimulus presented through headphones. The phase difference of the rotation and sound will be changed between trials. To evaluate whether the perception of simultaneity can be recalibrated, subjects will be exposed to a pre-determined, asynchronous condition preceding each trial. Each participant will complete four blocks of trials - without exposure, exposure to synchronous stimuli, exposure to asynchronous stimuli with the rotation lagging slightly behind the sound, and exposure to asynchronous stimuli with the sound lagging slightly behind the rotation.
Results: Preliminary auditory-vestibular data has not shown a consistent effect of asynchronous exposure on simultaneity judgment as of yet. However, the validity of using auditory-visual controls to serve as a reference point is being evaluated, since a measurable effect of auditory-visual recalibration has already been shown by several groups. Once it is confirmed that subjects, or at least a subset of subjects, can be susceptible to auditory-visual recalibration, it is anticipated that these subjects will also be more likely to show effects of auditory-vestibular recalibration.
Conclusions: It is unknown whether the integration of vestibular and other sensory modalities can be recalibrated. This study is attempting to address this issue and to assess how adaptable the processing of vestibular input is. While a conclusion cannot yet be drawn from this study, it will be important to continue to assess the plasticity of this type of multisensory integration, as there may be several clinical implications.

005 **Wright, Melissa A**
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Mentor: John A Curci, MD, FACS
Effect of lipid exposure on matrix metalloproteinase activity in AAA derived smooth muscle cells
Wright MA; Curci JA
Introduction: In the US, abdominal aortic aneurysms (AAAs) occur in 4-8% of older men and 0.5-1.5% of older women, causing about 12,000 deaths annually. With cholesterol exposure *in vitro*, vascular smooth muscle cells (VSMC) can take up cholesterol, altering their morphology. VSMC can also express the elastolytic enzymes that predominate in AAAs, namely matrix metalloproteinases (MMP) 2, 9 and 12. This study will compare the growth and development of aneurysmal and normal VSMCs in the context of cholesterol exposure to determine differences in MMP production.
Methods: Lab derived human VSMC from AAA, carotid plaque (CEA), and normal aorta (NAA) were cultured with Cyclodextran Cholesterol Complex solution (CCC) or standard media. Conditioned media was harvested and analyzed for levels of MMP-2 and MMP-9 using ELISA and zymogram. Cell counts were done.
Results: ELISA data showed that in AAA and CEA cells, levels of MMP-2 did not differ between control and CCC treatment ($p=0.722$; $p=0.211$). NAA cells had lower levels of MMP-2 when treated with CCC ($p=.098$). MMP-2 was consistently highest is CEA cells. MMP-9 levels were too low to show more than potential trends. On zymogram gel, AAA and NAA had similar levels of MMP-2 for the control, but with CCC treatment, levels of MMP-2 were higher in AAA cells. CEA levels of MMP-2 were high and showed random variation. MMP-9 levels were too low for analysis. Cell counts showed no difference in growth among the cells with control media ($p=0.616$). The growth of CEA cells when treated with CCC was higher than CCC treated AAA and NAA cells ($p=0.033$) and control CEA cells ($p=0.0128$).
Conclusions: Cholesterol exposure affects MMP production by VSMCs in varying ways depending on the origin of the VSMC and the MMP in question. CEA cells produce more levels of MMP-2 than any VSMC, independent of CCC treatment. While AAA cells produce less MMP-2, cholesterol does effect production. More sensitive techniques are needed to study levels of MMP-9. Overall, a better understanding of the complex effects of cholesterol on VSMC growth and MMP production will improve our understanding of AAA and carotid plaque pathogenesis.

006 **Yang, Zao**

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Mentor: Traves Crabtree, MD

Comparison of patterns of recurrence of clinical stage 1 non small cell lung cancer treated with surgery versus stereotactic body radiation therapy

Yang Z; Crabtree T

Introduction: The standard of care for low surgical risk patients with early stage lung cancer is surgical resection. Many patients with early stage lung cancer are considered inoperable due to poor pulmonary function or other co-morbidities, and stereotactic body radiation therapy is an alternative local treatment option. This study compares outcomes between stereotactic body radiation therapy and surgical treatment of non-small cell lung cancer.

Methods: We compared patients treated with surgery or stereotactic body radiation therapy from June 2004 to December 2010 with clinical stage IA/B non-small cell lung cancer staged by computed tomography and positron emission tomography. Charts were reviewed to determine local, regional, and distant tumor recurrence, disease-specific survival, and overall survival.

Results: The study cohort consists of 800 surgery patients and at least 217 stereotactic body radiation therapy patients. We expect surgical patients to be younger, have fewer co-morbidities, and better pulmonary function. In an unmatched comparison, we expect patients treated with surgery to have higher rates of survival. We expect this difference to be diminished when adjusted for co-morbidities.

Conclusions: This study should provide a valuable comparison of site-specific recurrence rates between these treatment modalities and serve as a foundation for future studies regarding the relative benefit of these therapies and the characteristics that classify patients as high risk in the current era of lung cancer treatment.

131 **Yen, Peter**

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Differences in inter-hemispheric functional brain connectivity among regions of the primary motor cortex

Yen P; Carter A

Introduction: Current stroke studies employing functional connectivity have elucidated that damage at a focal brain lesion has effects on activity at other, distant areas in the brain. This has been realized in activation of homologous regions following brain injury. Recent work has shown decreases in inter-hemispheric functional connectivity in the motor cortex correlates with motor impairment post-stroke. However, no studies have addressed the existence of differences within sub-regions of the motor cortex. The purpose of this study is to determine whether or not these distinct motor areas do differ in the strength of their functional connectivity.

Methods: Resting state functional imaging of healthy patients was conducted. Regions of interest in the motor cortex were determined in two ways: 1) a meta-analysis of recent studies using fMRI for several different bilateral motor movements and 2) a tiling procedure that mapped ROIs along the entire motor cortex. rsFC scores were calculated to determine inter-hemispheric connectivity strength, which was then compared among motor regions.

Results: Inter-hemispheric functional connectivity along the motor cortex showed a pattern of several high and one low connectivity scores consistent across subjects. However, there was a large standard deviation of scores in each region, across subjects. When comparing the location of these peaks to ROIs of motor regions generated in our meta-analysis, the foot and ankle ROIs located at the top of the medial portion of the brain corresponded to a peak score, the finger ROI located on the lateral portion corresponded to a large trough value.

Conclusions: From our inter-hemispheric functional connectivity data, there is evidence to support differences in connectivity among sub-regions of the motor cortex. Although areas with increased connectivity do not seem correspond with the degree of lateral-izability of movements, any conclusions require more work to corroborate our results. We plan to bring subjects back in to complete localizer scans for motor movements so that we can obtain accurate ROIs for target areas of the motor cortex.

T35 NIH NIDDK Short-Term Training Program

091 **Baker, Alexandra H**
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Division of Infectious Disease
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Mentor: David Haslam, MD
The role of MK2 in response to *Clostridium difficile* Infection
Baker AH; Haslam DB
Introduction: *Clostridium difficile* infection (CDI) is the most common hospital-acquired infection and can lead to GI disease ranging from mild diarrhea to toxic megacolon, sepsis, and death. The disease results from toxin-mediated damage to the gut and ensuing inflammatory response. In preliminary experiments, it was shown *in vitro* that *C. difficile* toxin activates a pro-inflammatory cascade mediated by the stress sensing kinase p38 and its downstream activator MK2. The aim of this study was to further characterize the role of MK2 in CDI mediated inflamation.
Methods: The first part of the study looked at the activation of MK2 after infection with *C. difficile* both *in vitro* and in intestinal epithelium of mice. MK2 knock out mice were then compared to a WT model of CDI. Mice were monitored for signs of disease and weight loss. Cytokine ELISA, Flowcytometry and qRT-PCR of both mouse colon and fecal samples were performed.
Results: MK2 was shown to be activated *in vitro* in response to CDI, and immunofluorescence staining demonstrated the activation of MK2 in the intestinal epithelial cells of infected mice. MK2 deficient mice were shown to have increased mortality and weight loss during infection, as well as increased neutrophilic and CD4+ cell infiltrate. Inflammatory cytokines had increased upregulation in MK2 intestinal epithelial cells and stool. While CD4+ cells were increased overall in MK2 deficient mice, the number of Th17 and IL-22 producing cells was markedly decreased when compared to WT.
Conclusions: While MK2 has been described as a pro-inflammatory mediator, this project shows that it is necessary for partially attenuating inflammation caused by CDI. The decrease in Th17 and IL-22 producing cells in the intestinal epithelium suggests that MK2 has a role in the differentation of CD4+ T cells into Th17 cells. Th17 and IL-22 have been shown to induce the production of defensins, mucins and other transcription factors involved in epithelial cell repair and proliferation, as well as microbial clearance. The next step in this project should be to investigate the possible protective role of Th17 cells in *C. difficile* infection to help improve the management of this increasingly pervasive disease.

No Poster Displayed

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Mentors: Rachel Kolko, MA; Denise Wilfley, PhD
Role of network support on family based treatment outcomes among overweight children
Bitow N; Kolko R; Stein R; Wilfley D
Introduction: Family-based behavioral weight loss treatment (FBT) is an evidence-based intervention that yields significant weight loss among both adult and pediatric overweight populations. FBT aims to decrease children's engagement in obesogenic activities and increase their engagement in healthy behaviors related to physical activity and dietary habits. Network support among study participants was assessed using the Network Support and Healthy Behaviors (NSHB) interview. The current study aims to explore the role of network support for obesogenic and healthy behaviors on FBT outcome among overweight and obese children (*N*=186) who completed treatment and assessment of network support.
Methods: Child-parent dyads (n=241) were enrolled in a weight management, randomized control trial, COMPASS Study, conducted in St. Louis, MO (Washington University) and Seattle, WA (Seattle Children's Hospital). Participants completed a 16-week FBT intervention that involved weekly group and individual sessions. Children that completed FBT and the baseline NSHB assessment were included in the present study (n=186). Age, gender, race/ethnicity, socio-economic status, baseline and post-FBT percent overweight, and baseline network support variables were assessed for the present study.
Results: It is anticipated that there will be a significant association between network support and FBT weight loss outcome such that, children with higher levels of network support for healthy behaviors will exhibit greater reductions in percent overweight following FBT than those with lower levels of support. Conversely, children with higher levels of network support for obesogenic behaviors will exhibit less significant weight loss.
Conclusions: There is a critical need for the development of effective treatments and an understanding of the factors that influence weight loss and management in pediatric populations. A positive association between network support and FBT weight loss would support the need for further research to explore how social network mediates and can be incorporated into weight loss programs aimed at pediatric populations.

049 **Chen, Lu**

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Mentor: Kerry Kornfeld, MD, PhD

Population dynamics of *C. elegans*

Chen L; Kornfeld K

Introduction: C. elegans is a well-established developmental and genetic model organism. Life history traits like aging have been well characterized genetically, but the effects of these traits on population dynamics is less clear. The purpose of this study is to measure the life history traits of *C. elegans* and use them to create a mathematical model that predicts the population dynamics of each strain and establish a relationship between life history traits and fitness.

Methods: To achieve this, wild-type *C. elegans* were grown in liquid culture, allowing for larger populations, and fed periodically so that they experienced cycles of feeding and starvation. In addition, worms were periodically removed from the population to simulate predation or other dangers in the environment. A COPAS worm sorter was used to count a portion of the worms removed and measure their lengths. By taking into account the characteristics of their environment, as well as life history traits such as lifespan and progeny production, a population model was developed.

Results: Life history data will be collected. The methodology for growing *C. elegans* in liquid culture is currently being improved, but there is preliminary data that shows population fluctuations, as expected. The framework for a mathematical model has been established, and oscillations can be observed. Once life history data is collected, it will be used as input into the mathematical model, which will then be fit to and compared with the measured population counts.

Conclusions: This work will allow better understanding of how life history traits affect population dynamics and form an experimental basis to test these kinds of hypotheses. This will give further insights to the effects of aging. Future work involves varying food and predation or studying different *C. elegans* mutant strains that possess life history traits different from wild-type worms in order to test the robustness of the population model and further elucidate the relationship between life history and population dynamics.

054 **Cooks, Tammi**

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Program for the Elimination of Cancer Disparities (PECaD)
Siteman Cancer Center, Washington University in St. Louis School of Medicine
Mentors: Aimee James, Ph.D; Kristen Massey, MPH, CHES; Graham Colditz, MD, DrPH

Routes to care: mapping out colorectal cancer care for un/underinsured in St. Louis

Cooks T; James A; Massey K; Colditz G

Introduction: Colon cancer is the third most common cancer diagnosis in the United States and the third leading cause of cancer-related deaths. For these reasons, access to preventative screening is very important for patients. Access can be an issue for many individuals and can contribute to cancer disparities that exist amongst patient populations. Realizing that navigating through the healthcare system can be less than straightforward, I wanted to place a special emphasis on low-income and un/underinsured patients and examine referral processes that these patients have to navigate.

Methods: Community-based participatory research principles and qualitative research methods in collaboration with the Colorectal Cancer Community Partnership of the Program for the Elimination of Cancer Disparities (PECaD) at the Alvin J. Siteman Cancer Center of Barnes-Jewish Hospital and Washington University School of Medicine

Results: Anticipated results will include clarity and definition of referral processes being used. Potential dissemination tools are 1) a multi-level flow chart that maps out referral processed for colorectal cancer care among low-income and un/underinsured patients in the St. Louis metropolitan area, and 2) a resource guide that helps guide patients and providers to resources that can aid in the referral process.

Conclusions: Data collection is still in progress, therefore final conclusions are pending.

014 **DeSanto, Cori**
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Mentors: Nikkilina R. Crouch PhD; David H. Gutmann MD, MPH
Differential activation and composition of the mTOR Complex in *Nf1*, Pten, and *Tsc1*-deficient astrocytes
DeSanto CL; Crouch NR; Gutmann DH
Introduction: The mammalian target of rapamycin (mTOR) is a regulator of astrocyte growth that exhibits increased activation in gliomas, a form of brain cancer. Previous work has demonstrated that inactivation of the neurofibromatosis-1 (*Nf1*), Pten, and tuberous sclerosis complex-1 (*Tsc1*) tumor suppressor genes result in differential activation of the mTOR complex. Furthermore, different levels of the mTOR components raptor and rictor are expressed in primary astrocytes compared to neural stem cells and fibroblasts. It was hypothesized that the mechanism of mTOR activation and the molecular species assembled in the mTOR complex determine the biological effects of mTOR function.
Methods: To determine what molecules are responsible for mTOR activation, *Nf1 +/+* and *Nf1-/-* astrocyte lysate was generated and the *Nf1* knockout was confirmed by Western blot. Activation of upstream signaling molecules will be detected by mass spectroscopy. To determine the molecular composition of mTOR in the absence of *Nf1*, protein was extracted from *Nf1*-deficient 4622 glioma cells. The mTOR complex was isolated from 4622 cell lysate by immunoprecipitation, and the samples will be sent for mass spectroscopy analysis.
Results: All samples will be sent to collaborators for mass spectroscopy pending collection of sufficient protein and confirmation of mTOR pulldown by Western blot.
Conclusions: Based on the results of these preliminary experiments, similar procedures will be carried out in wild type, *Nf1-/-, Tsc1-/-,* and *Pten-/-* astrocytes to compare the species assembled in the mTOR complex and the molecules activated in response to tumor suppressor loss. These experiments are aimed at elucidating the mechanism of mTOR regulation in order to identify improved targets for brain cancer drug therapies.

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Physical activity and gastric cancer risk: a meta-analysis
Hartzell G; Wolin K
Introduction: Gastric cancer is the fourth most common cancer and the second leading cause of cancer deaths worldwide. It is significantly more common in Asia and Eastern Europe than the United States, and research into various risk factors is still minimal. Although some causes have been determined, the etiology of gastric cancer is not completely understood. Recent studies have shown a significant correlation between physical activity and a reduced incidence of other GI cancers, such as colon or colorectal cancer. This meta-analysis seeks to determine if gastric cancer risk is similarly impacted by physical activity level.
Methods: A PubMed search was conducted to collect data from all relevant studies looking at physical activity and gastric cancer risk. Meta-analysis of random effects was used to compare results across studies. Standard errors were calculated and were used as weights for summary effect estimates in the meta-analysis.
Results: Overall a small but significant relationship was found. We found a significant inverse association between physical activity and gastric cancer risk (random effects OR/RR/HR -0.18, 95% CI: -0.30 - -0.07). The effect of physical activity was more pronounced in studies that stratified more by physical activity level, indicating a possible dose-response relationship.
Conclusions: Because of the significant global public health impact of gastric cancer, it is important to understand the risk factors contributing to this disease, and possible steps that can be taken to prevent it. Theories for the impact of physical activity on cancer risk include improved immune function and a decrease in inflammatory and growth factors that might contribute to malignancies.

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Observational study of stool bacterial populations in children at risk for malnutrition

Humbert M; Manary M

Introduction: This study aims to identify patterns in bowel flora that are associated with Kwashiorkor among toddlers in Sub Saharan Africa.

Methods: Stool samples were collected from healthy Malawian twins every 3 months from 0 to 36 months of age. Stool samples were also collected from the mother and a sibling of the twins as controls. Nutritional statuses of the twins were monitored through monthly visits to local health centers. Malnourished children were treated with nutritional therapy and additional stool samples were collected from both the malnourished child and the healthy twin at 2, 4, 8, and 16 weeks following recovery. Bacterial rRNA will be isolated from the stool and analyzed to identify and quantify the major types of bacteria present by the J.I. Gordon lab at Washington University.

Results: 317 twin pairs were initially enrolled. Samples have been collected through 36 months for 151 twin pairs. 75 twin pairs have been lost to follow up or disqualified (death of one of the twins). Samples are currently being collected from the remaining 75 twins.

Conclusions: It is expected that changes in both bacterial diversity and population foreshadow the onset of kwashiorkor.

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Differences in miRNA expression across varying grades of gliomas

Joshi N; Kuchenreuthe; MJ; Weber J

Introduction: Approximately 3 of every 100,000 people in the U.S. will develop a glioma, but the prognosis depends greatly on the WHO tumor grade. Whereas pilocytic astrocytomas (grade II) have 10-year survival rates over 90% following complete resection, glioblastomas (grade IV) have 10-year survival rates of approximately 3%. Understanding what genetic basis there might be for such starkly different outcomes could help guide research into therapeutic options for patients with high grade gliomas. We chose to look specifically at miRNA expression as changes in their silencing effects could have potentially significant downstream effects on tumor behavior. We expected to see some miRNAs expressed at significantly different levels in low versus high grade gliomas.

Methods: We isolated RNA from four primary glioma samples (two each of grade II and grade IV). This RNA was converted to cDNA and run in a Megaplex qRT-PCR reaction, probing for various human miRNAs.

Results: We found that, of the miRNAs we looked at, miR-200a, miR-133b, and miR-10a were all expressed at a much higher rate in high grade gliomas.

Conclusions: MiR-200 and miR-10 are already known to have relevance to tumors and are thus the most promising of the miRNAs we looked at. In the future, we would like to alter the expression of these miRNAs to see if they have any causative effect on tumor differentiation.

103 **Kim, David H**

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Characterization of phenoxazine derivatives for cerebral amyloid angiopathy imaging

Kim D; Zipfel G; Han H

Introduction: Cerebral amyloid angiopathy (CAA) is defined by amyloid deposition within walls of leptomeningeal and cortical arterioles. CAA is a well recognized cause of cerebral hemorrhage, and is also a known contributor to ischemic stroke and cognitive impairment. Definitive diagnosis of CAA can currently only be obtained via brain biopsy or autopsy. The development of a precise and specific non-invasive technique for diagnosing CAA in live patients is therefore desirable. The hypothesis is that phenoxazine derivatives serve as a unique CAA-selective amyloid imaging probe that will permit non-invasive diagnosis of CAA, quantitation of CAA severity, and monitoring of CAA progression over time.

Methods: Cerebrovascular vessel isolates from 18 month old APPsw mice were prepared via centrifugation. The vessel isolates were stained with phenoxazine derivatives and quantified via a fluorescence assay to determine binding affinity for vessels. Tissue sections from 18 month old APPsw mice were also stained with phenoxazine derivatives to determine specificity for neuritic vs. vascular amyloid plaques.

Results: Multiple phenoxazine derivatives were tested with the fluorescence binding assays. Few phenoxazine derivatives were found to have high specificity and high affinity for CAA plaques. The results are inconclusive because many compounds tested had negligible fluorescence, which made quantification of affinity or selectivity difficult. Although the optimal phenoxazine derivative's specificity for plaques is sufficient, the binding affinity must be improved upon for use as an imaging probe in human subjects. Future work will be completed along these lines with more derivatives and radiological assays.

Conclusions: CAA is a very common disorder, pathologically affecting about one-third of all elderly patients (> 60 years of age) and about 90% of patients with AD. The development of phenoxazine derivatives as candidate imaging probes for this condition would allow diagnosis in live patients and open the door to future therapeutic interventions.

002 **Kyllo, Rachel**

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Multi-center intermediate-term oncologic outcomes of robot assisted partial nephrectomy for pT1 renal cell cancer

Kyllo RL; Kaouk J; Stifelman M; Rogers C; Hillyer S; Sukumar S; Tanagho Y; Nepple KG; Bhayani SB

Introduction: Partial nephrectomy has been increasingly recommended over radical nephrectomy for the management of small renal masses based on improved renal function outcomes without sacrificing oncologic effectiveness. Robotic assisted partial nephrectomy (RAPN) has been introduced in an effort to offer another minimally invasive option for nephron-sparing surgery. However, reports of RAPN have been limited by the lack of extended follow-up. Therefore, we sought to evaluate oncologic outcomes of RAPN for small renal masses by pooling a multi-institutional experience.

Methods: Utilizing prospectively obtained data on RAPN performed by 4 surgeons at four separate tertiary care centers, we selected patients with unilateral localized non-familial pathologically-confirmed pT1 renal cell carcinoma and a minimum post-operative follow-up of 12 months. Survival analysis (disease-free, cancer-specific, and overall survival) was performed and Kaplan-Meier curves were generated.

Results: RAPN was performed in 124 patients with a median tumor size of 3.0 cm (IQR 2.2-4.2 cm). Median follow-up was 29 months (range 12-46 months). Positive parenchymal surgical margin occurred in 2 patients (1.6%), both of whom were recurrence-free at 30 and 34 months after surgery. The 3-year Kaplan-Meier estimated disease-free survival was 94.9%, cancer-specific survival was 99.1%, and overall survival was 97.3%.

Conclusions: In our cohort of patients with small renal carcinomas who were followed for a median of 29 months, recurrence and survival outcomes were similar to those reported for open and laparoscopic partial nephrectomy. Further long-term outcomes will be needed to definitively claim that RAPN is oncologically equivalent to other surgical approaches.

036 **Liu, Lucy**

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Half-life of human SOD1

Liu L; Munsell LY; Winer LK; Bateman RJ; Miller TM

Introduction: Mutations in the gene for superoxide dismutase 1 (SOD1) account for 20% of dominantly inherited amyotrophic lateral sclerosis (ALS) cases. These genetic mutations ultimately produce proteins with toxic properties. A SOD1 mRNA antisense oligonucleotide has been designed to inhibit SOD1 production, lower SOD1 protein levels in the brain and spinal cord, and limit disease progression. Decreased SOD1 in brain and spinal cord is reflected in decreased SOD1 in the cerebral spinal fluid (CSF). Thus, CSF SOD1 can be used as a biomarker for the effectiveness of this antisense oligonucleotide. Normal SOD1 production and clearance is needed to determine efficacy in human patients. We hypothesized that the SOD1 half-life in human CSF samples could be determined using a technique developed by Bateman et al. involving $^{13}C_6$-leucine labeling and high-resolution tandem mass spectrometry.

Methods: CSF samples were previously obtained from healthy volunteers after administration of a stable isotope-labeled amino acid ($^{13}C_6$-leucine). Samples were taken at 1-hour time intervals for 36 hours.

Results: We successfully developed a method for immunoprecipitation of the SOD1 protein from CSF followed by high-resolution tandem mass spectrometry to quantify the amount of labeled and unlabeled SOD1 present in each sample.

Conclusions: After 36 hours, $^{13}C_6$-leucine labeled SOD1 levels continued to rise. Because SOD1 is an intracellular protein, this result suggests that cells secrete SOD1 into the CSF at a very low rate or that the half-life of SOD1 is very long (many days to weeks). Therefore, the SOD1 half-life is not quantifiable with time points under 36 hours. Future studies will look at production and clearance of mutant and wild-type SOD1 in rats and using pharmacokinetic algorithms to convert to human values.

075 **McGuiness, Phillip A**

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Correlation in mid-upper arm circumference and change in weight-for-height z-score among children treated for moderate acute malnutrition in Malawi

McGuiness PA; Manary M

Introduction: Each year more children die from moderate than severe malnutrition. Home-based therapy using ready-to-use supplementary foods has proven to successfully treat uncomplicated childhood moderate acute malnutrition (MAM) on an outpatient basis. This study attempts to discern if mid-upper arm circumference (MUAC) measurements collected by community-based health aides have the potential to monitor changes in nutritional status among moderately malnourished Malawian children while undergoing therapy.

Methods: Retrospective analysis is being performed using the anthropometric data of 4600 moderately malnourished children during treatment who have been cared for over the last 5 years. Changes in MUAC and changes in overall weight and WHZ at 1 and 2 months of treatment are being compared. Various geometric relationships are being explored between the measures to find the most direct and predictive relationship. The influence of a variety of covariates, such as age or gender, on the relationship between a child's change in MUAC and his/ her change in WHZ is also being explored. From these data, models will be developed to investigate anthropometric changes in children undergoing treatment.

Results: The models developed may provide a technique by which recovery from MAM could be monitored by village health aides in low resource settings using MUAC alone, greatly improving the accessibility of patient tracking and follow up.

Conclusions: The models developed may provide a technique by which recovery from MAM could be monitored by village health aides in low resource settings using MUAC alone, greatly improving the accessibility of patient tracking and follow up.

No Poster Displayed

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Ten years of shockwave lithotripsy and limitations experienced at a Tertiary Referral Center

Okunbor O; Benway BM; Fingenshau RS; Bhayani SB; Desai AC

Introduction: Over time, several variables have been recognized as limitations for shockwave lithotripsy (SWL) treatment for urolithiasis. The nature of patients referred to tertiary centers may reflect these limitations, serving as a unique challenge for SWL. We evaluated the characteristics of patients referred to our institution for SWL.

Methods: Over 4,200 SWL procedures performed from 1999-2009 were retrospectively reviewed. The only inclusion criteria for this study were patients who had received SWL treatment for urolithiasis. Body mass index (BMI) was calculated and evaluated for all years. Stone composition from chemical analysis per available stone was evaluated according to the predominant component, with a focus on early years (2001, 2002) and years (2007-2009).

Results: BMI ranged from 28-30, remaining stable with no statistically significant variation from year to year. Surprisingly, stone composition throughout was predominately calcium oxalate monohydrate, followed by calcium phosphate. Calcium oxalate dihydrate accounted for $\leq$10% of all stones in each year evaluated.

Conclusions: It is evident that calcium oxalate dihydrate has consistently been the predominant component in an overwhelming percentage of stones being treated; while a stable BMI of 28-30 illustrates a borderline obese patient population. The stone composition and BMI represented in this population over 10 years reflects unfavorable limitations that have been proven to significantly reduce the efficacy in SWL. The unique nature of our institution serving as a referral center for SWL may influence the characteristics of urolithiasis patients we are sent that render them unfit for SWL treatment.

076 **Ostendorf, Katelyn**
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Comparing milk fortified corn/soy blend, soy/peanut fortified spread, and supplementary plumpy® in the treatment of moderate acute malnutrition in rural Malawian children. Long term follow up of children treated for moderate acute malnutrition in Malawi

Ostendorf K; Trehan I; Manary M

Introduction: Moderate acute malnutrition (MAM) affects over 10% of children globally and is associated with significant morbidity/mortality. Understanding the effectiveness of various therapeutic food treatments is crucial. This study aims to determine if the foods used to achieve recovery from MAM in children affect the likelihood of relapse over the course of one year by comparing the clinical effectiveness of CSB++, locally produced soy RUSF, and imported soy/whey RUSF in preventing relapse by following the children who have recovered from MAM for 12 months after the completion of supplementary feeding.

Methods: This study is a randomized, investigator-blind, controlled trial that compares the clinical effectiveness of CSB++, locally produced soy RUSF, or imported soy/whey RUSF in preventing relapse upon recovery from MAM by following the subset of children who recovered from MAM following the initial intervention. The primary outcome is the proportion of children who never relapse within 12 months following the successful completion of therapeutic supplementary feeding from MAM. Secondary outcomes are the proportion of children who never relapse by 3 or 6 months and the proportion who recover from relapse following a second round of supplementary feeding. Intention-to-treat analysis will be used, and proportions of primary and secondary outcomes in the three food groups will be compared using Chi-squared tests. A probability of <0.05 will be considered to be statistically significant.

Results: At this time in the ongoing study, 2,219 of the expected 2,295 children have completed the study protocol. Differences in supplementary food type are not expected to be associated with relapse rate after treatment for MAM because no significant differences were found between the initial MAM recovery rate for children treated with CSB++ (85.9%) versus soy and soy/whey RUSF (87.7% and 87.9% respectively).

Conclusions: If the results of this study confirm that CSB++ is equally as effective at preventing relapse from MAM as both RUSF varieties, then it may help provide global agencies and health services with guidance as to how to most efficiently treat MAM.

No Poster Displayed

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Alpha and beta adrenergic receptor blockade prolongs onset of severe hypoglycemia-induced cardiac arrhythmias
Rich R; Reno C; Daphna-Iken D; Fisher S

Introduction: Otherwise healthy individuals with Type 1 diabetes have been found 'dead-in-bed' with no clear cause of death. Insulin-induced severe hypoglycemia has been confirmed to be associated with this 'dead in bed' syndrome by causing fatal cardio-respiratory arrest, leading to the question of whether increased catecholamine surge leads to increased risk for fatal cardiac arrhythmias. The purpose of this study is to examine if blocking adrenergic receptor signaling will reduce QTc prolongation, cardiac arrhythmias, and death due to severe hypoglycemia.

Methods: Rats were divided into saline infused control and combined alpha and beta adrenergic receptor blockade groups. Catheters were inserted into the carotid artery and jugular vein, and EKG recording electrodes were placed under the skin in anesthetized rats. Rats were then subjected to hyperinsulinemic severe hypoglycemic clamps and infused with either saline (CON) or a combined alpha and beta adrenergic receptor blockade (Blockers).

Results: Onset of severe hypoglycemia-induced cardiac arrhythmias was prolonged in the Blockers group as compared to the CON group. Average heart rate during severe hypoglycemia for Blockers rats was lower by 25%* than that for CON rats. QTc interval length between CON and Blockers was not significantly different. Average respiration rate during severe hypoglycemia was lower by 27%* for Blockers as compared to CON. *$p < 0.05$, two-way ANOVA.

Conclusions: Continuous EKG recordings support the notion that fatal cardiac arrhythmias in the setting of insulin-induced severe hypoglycemia are major mediators of the 'dead in bed' syndrome, highlighting the importance of exploring the mechanisms involved. It is proposed to expand on these preliminary findings and determine the mechanism by which decreased heart rate, shortened QTc interval, decreased respiratory rate, or a combination of all three factors appear to prolong onset of cardiac arrhythmias. Prevention of severe hypoglycemia-induced cardiac arrhythmias has potential to contribute to prevention of death in the 'dead in bed' syndrome.

020

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Decreased microstructural integrity of white matter in children with PKU: a DTI study
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Introduction: Phenylketonuria (PKU) is an autosomal recessive disorder characterized by defective metabolism of the amino acid phenylalanine (Phe) that eventually leads to a deficiency of dopamine. PKU is associated with cognitive deficits and recent studies have identified brain abnormalities in PKU patients, especially in white matter. Diffusion tensor imaging (DTI) allows for the evaluation of the microstructural integrity of white matter tracts in the brain. Two DTI measures are usually reported: the apparent diffusion coefficient (ADC) and fractional anisotropy (FA). ADC is a measure of the rate of water diffusion, while FA is a measure of the asymmetry of water diffusion. The purpose of this study is to investigate the integrity of white matter in the brain of children suffering from PKU as a possible reason for the cognition impairments seen in this disorder.

Methods: Children with PKU and age- and gender-matched controls were recruited and scanned with a 1.5T scanner. Images acquired include T1-weighted sagittal, magnetization prepared rapid gradient echoes, T2-weighted fast spin echoes, and DTI images. The scans were then registered to the same atlas to allow for comparison. Lastly, the program Analyze was used to calculate the ADC and FA values for 14 different areas of interest in the brain.

Results: Using rigorous statistical testing, the FA and ADC for each area of interest when compared between the PKU and control groups. No area of interest showed a difference in FA between the PKU and control groups, while ten of the fourteen measured areas showed a decrease of ADC in the PKU subjects.

Conclusions: The observed results imply that while the water molecules in the brain move along white matter tracts as one would expect, they move much more slowly in the brains of PKU subjects. One hypothesis for this phenomenon is that debris from the inadequate metabolism of Phe collects in the white matter slowing diffusivity. This and other interesting aspects of PKU will be further studied with the continuation of this project.

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Regulatory effects of alpha-synuclein on long chain Acyl-CoA synthetases

Yuan KZ; Kotzbauer PT

Introduction: Alpha-synuclein is normally a soluble protein that is thought to be involved in vesicle trafficking and brain lipid metabolism, however its exact actions are unknown. Dominant mutations in the alpha-synuclein gene cause rare familial versions of Parkinson's disease and mis-folded alpha-synuclein can aggregate to form fibrils that result in the formation of Lewy bodies, the pathological structures that are the defining feature in Parkinson's disease. It has been reported that alpha synuclein is involved in lipid metabolism in the brain, and in particular it seems to play a role in the reaction catalyzed by acyl-CoA synthetase. The hypothesis is that the alpha-synuclein protein promotes the activity of long chain acyl-CoA synthetase in vitro, while mutated alpha-synuclein, that is associated with familial Parkinson's disease, will show an altered interaction with the acyl-CoA synthetase.

Methods: The interaction between alpha-synuclein and long chain acyl-CoA synthetase will be studied using an enzyme assay with radiolabeled substrate. Long chain acyl-CoA synthetases will be incubated with radiolabeled fatty acids, and both with and without alpha-synuclein. The end product of the reaction in question will be radiolabeled acyl-CoA; the amount of product will be determined at various time points using thin layer chromatography.

Results: It is expected that alpha synuclein will promote the activity of the three long chain acyl-CoA synthetases, while the mutated alpha-synuclein will either show less of a promoting effect or none at all.

Conclusions: This experiment will help elucidate the normal functions of alpha-synuclein in lipid metabolism, which will aid in the understanding of its role in the pathophysiology of diseases such as Parkinson's disease.

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Abstract Authors

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