27th Annual Research Forum

Thursday, April 16, 2009
2:00pm - 4:45pm
208 Light Hall

Established and Sponsored by the Vanderbilt University House Staff Advisory Council
Vanderbilt University Medical Center’s Research Forum provides an opportunity for non-faculty VUMC personnel to present research conducted at Vanderbilt. This Forum is open to all Vanderbilt University House Staff and Medical Students.

Research must have been performed at Vanderbilt. Unpublished work is eligible and encouraged. Work already published, or presented at another meeting, is also eligible and encouraged. All submitted abstracts are published in the Vanderbilt University Medical Center Research Forum book.

Abstracts are reviewed and selected for either an oral or a poster presentation by a panel of Vanderbilt School of Medicine faculty members who are actively involved in clinical and basic science research. There are six abstracts selected for oral presentation—three in Basic Science Research and three in Clinical Research. After the oral presentations at the Forum, the best overall project in each category (Basic Science Research and Clinical Research) will be awarded an Elliot V. Newman Award.

The Grant W Liddle Award, which honors a faculty member who demonstrates exemplary leadership in the promotion of scientific research at Vanderbilt University Medical Center, is presented annually at the Forum. Additionally, Vanderbilt School of Medicine students present the Davies, Brittingham, Hillman and Resident Teaching Awards which honor faculty and house staff teaching excellence.
TWENTY-SEVENTH ANNUAL RESEARCH FORUM

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Clinical Fellow, Cardiovascular Medicine Division

AND

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Resident, Department of Surgery

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Division of Clinical Pharmacology
Department of Medicine & Pharmacology
GRANT W. LIDDLE AWARD

The Grant W. Liddle Award was established in 1983 by the Vanderbilt University Medical Center house staff to recognize faculty members who demonstrate exemplary leadership in the promotion of scientific research at the Vanderbilt University Medical Center.

A native of American Folk, Utah, Dr. Liddle graduated first in his class from the University of Utah in 1943. After obtaining an M.D. degree from the University of California, San Francisco, in 1948, he served as a post-doctoral fellow at the newly formed Metabolic Research Unit at the NIH. In 1956, Dr. Liddle was recruited by Dr. Hugh J. Morgan to become Director of Endocrinology at Vanderbilt University. He was named Chairman of the Department of Medicine in 1968, a position he held until 1983.

Dr. Liddle’s career was marked by commitment to excellence in research, patient care, and the teaching of house staff and medical students. His research accomplishments include developing the dexamethasone suppression test and metyrapone test for assessing pituitary-adrenal gland function; describing a new form of hypertension, pseudohypoaldosteronism (Liddle’s Syndrome); developing spironolactones as useful aldosterone antagonists; and systematically improving methods for treating Cushing’s disease. In 1982, he was elected to the National Academy of Sciences and to the Royal College of Physicians in England.

Past Recipients of the Grant W. Liddle Award are:

2008 Dennis Hallahan, M.D.
2007 Nancy J. Brown, M.D.
2006 Adrian Jarquin-Valdivia, M.D., R.D.M.S.
2005 Marshall L Summar, M.D.
2004 Denis M. O’Day, M.D.
2003 Herbert S. Schwartz, M.D.
2002 John A. Zic, M.D.
2001 Kathryn M. Edwards, M.D.
2000 R. Michael Rodriguez, M.D.
1999 David H. Van Buren, M.D.
1998 Charles Wright Pinson, M.D., M.B.A.
1997 Steven Leach, M.D.
1996 Jason D. Morrow, M.D.
1995 Robert H. Ossoff, M.D., Ph.D.
1994 William O. Richards, M.D.
1993 Barney S. Graham, M.D.
1992 Gordon Bernard, M.D.
1991 Achilles Demetrious, M.D., Ph.D.
1990 David Robertson, M.D.
1989 Robert Collins, M.D.
1988 Stanley Cohen, Ph.D.
1987 John A. Oates, M.D.
1986 David T. Karzon, M.D.
1985 Naji N. Abumrad, M.D.
1984 Fayez K. Ghishan, M.D.
1983 Grant W. Liddle, M.D.
THE ELLIOT V. NEWMAN PRIZE

Elliot Voss Newman was a distinguished cardiologist, scientist, medical scholar and teacher. A graduate of Harvard College and Medical School, Dr. Newman came to Vanderbilt from Johns Hopkins University in 1952 to establish a program of clinical physiology and research. The author of the electrocardiography chapter in Harrison’s Textbook of Medicine and of the renal physiology chapter in Cecil and Loeb’s textbook, Dr. Newman was a pioneer in the development of medical engineering and the use of applied mathematics and computer science for clinical problems. Dr. Newman was the first Joe and Morris Werthan Professor of Experimental Medicine at Vanderbilt and was founder of the Clinical Research Center, which bears his name. He was a friend and mentor to medical students and house officers alike and helped to promote the scientific careers of many.

Recent Elliot V. Newman Award recipients:

2008
Bradley J. Van Sickle, M.D., Ph.D. - Clinical Fellow, Pediatric Endocrinology
“Poor Glucose Control in Adolescents with Type 1 Diabetes is Associated with Increased IL-8 but Reduced IGF-1”

Shih-Hsin Eddy Yang, M.D., Ph.D. - Resident, Radiation Oncology
“Lithium Protects Hippocampal Calles by Enhancing DNA-PK-Dependent Nonhomologous End Joining of Radiation-Induced Chromosomal Breaks”

2007
Eitan Friedman, M.D. - VMS, Class of 2007
“The Effects of Tadalafil on Cold-induced Vasoconstriction in Patients with Raynaud’s Phenomenon”

Sachin Patel, M.D. - Resident, Psychiatry
“Endocannabinoid Signaling Modulates Dendritic Spine Density in Prefrontal Cortical Pyramidal Neurons”

2006
Siam Oottamasathien, M.D. - Clinical Fellow, Urology-Pediatric Urology
“Formation of Bladder Tissue from Embryonic Stem Cells”

Jennifer Schuberth, M.D. - Clinical Fellow, Internal Medicine
“Changes in Residency Work Hours: Impact of the Short Call Team on Length of Stay and Quality of Care for Heart Failure”

2005
Heidi A. Smith, M.D. - Clinical Fellow, Pediatric Critical Care
“Nitric Oxide Precursors and Congenital Heart Surgery: A Randomized Controlled Trial of Citrulline”

Fred Y. Wu, Ph.D. - VMS, Class of 2007
“A Paradoxical Role of p27 Tumor Suppressor: Reduction of Cytosolic p27\(^{kip1}\) Protein Decreases Akt Stability and Inhibits Cancer Cell Motility, Survival, and tumorigenicity”

2004
Jennifer Halpern, M.D. – Resident, Orthopaedics
“Evolution of an In Vivo Bioreactor: Vascularized Scaffold Generate Novel Host Bone”

Elisabeth D. Riviello. - VMS, Class of 2006
"HIV in Botswana:Saliva Test Validation, CD4 Cell Counts, Prevalence, and Incidence"
TWENTY-SEVENTH ANNUAL
VANDERBILT UNIVERSITY RESEARCH FORUM
Thursday, April 16, 2009 • 2:00 p.m. – 4:45 p.m. • 208 Light Hall

2:00 ............................................................................................................... OPENING REMARKS Josh Smith, MD
.......................... .......................................................... WELCOME Donald Brady, MD
............. PRESENTATION OF SURVEY DATA/ INTRODUCTION OF FORUM MODERATOR Susan Bell, MD
.............................................. FORUM MODERATOR Dennis Hallahan, MD

2:15 MECHANISM OF VASCULAR ENDOTHELIAL GROWTH FACTOR BLOCKADE INDUCED MYELOSUPPRESSION IN LUNG CANCER PATIENTS TREATED WITH ANTI-VEGF THERAPY Ildiko Csiki, MD, PhD; Sergey Novitsky, PhD; Mikhail Dikov, PhD; Alan Sandler, MD; David H Johnson, MD; David P Carbone, MD, PhD

2:30 INHIBITION OF GSK3β ENHANCES REPAIR OF RADIATION-INDUCED DNA DOUBLE STRAND BREAKS IN HIPPOCAMPAL NEURONS Eddy S Yang, MD, PhD; Somaira Nowsheen, MD; Dennis E Hallahan, MD, Fen Xia, MD, PhD

2:45 PROTEASE-ACTIVATED RECEPTOR (PAR-1) AGONIST PEPTIDE VASOCONSTRICTS CANINE EPICARDIAL CORONARY ARTERIES IN VIVO Kasasbeh, ES; Phillips SA; Liu Q; Krueger JG; Cleator JH

3:00 IMPACT OF CONDITIONING REGIMEN IN ALLOGENEIC HAMATOPOETIC STEM CELL TRANSPLANT FOR CHILDREN WITH AML BEYOND FIRST COMPLETE REMISSION: A PEDIATRIC BLOOD AND MARROW TRANSPLANT CONSORTIUM (PBMT) STUDY India Y Sisler, MD; Tatsuki Koyama, PhD; Elizabeth Koehler, MS; Jennifer A Dommm, MD; Robin Ryan, MPH; John E Levine, MD; Michael A Pulsipher, MD; Paula R Haut, MD; Kirk R Schultz, MD; Douglas S Taylor, MD; Haydar A Frangoul, MD

3:15 PARENTAL KNOWLEDGE AND USE OF PREVENTIVE ASTHMA CARE MEASURES Jamie N Deis, MD; David M Spiro, MD, MPH; Cathy A Jenkins, MS; Tamara L Buckles, MD; Donald H Arnold, MD, MPH

3:30 NOREPINEPHRINE TRANSPORTER POLYMORPHISMS AFFECT BLOOD PRESSURE RESPONSE TO EXERCISE Utkarsh Kohli, MD; Maureen K Hahn, PhD; Brett A English, PhD; Mordechai Muszkat, MD; Gbenga G Sofowora, MD; Randy D Blakely, PhD; C Michael Stein, MD; Daniel Kurnik, MD

3:45 EXCUSE JUDGES FOR DELIBERATION (RM. 213 LIGHT HALL) ................. Dennis Hallahan, MD

3:45 POSTER PRESENTATION AWARDS ................................................................. Josh Smith, MD & Susan Bell, MD

3:50 GRANT W. LIDDLE AWARD ................................................................. Michael Rosen, MD

3:55 ELLIOT V. NEWMAN AWARDS ............................................................. Dennis Hallahan, MD

3:55 INTRODUCTION OF KEYNOTE SPEAKER ........................................ Josh Smith, MD

4:00 KEYNOTE SPEAKER .................................................................................. Gordon Bernard, MD
Assistant Vice-Chancellor for Research
2009 ORAL PRESENTERS

ILDIKO CSIKI, M.D., Ph.D.
Resident, Radiation Oncology

EDDY S. YANG, M.D., Ph.D.
Resident, Radiation Oncology

EHAB KASASBEH, M.D.
Clinical Fellow, Cardiovascular Medicine

INDIA SISLER, M.D.
Clinical Fellow, Pediatrics

JAMIE N. DEIS, M.D.
Clinical Fellow, Emergency Medicine

UTKARSH KOHLI, M.D.
Clinical Fellow, Departments of Medicine and Pharmacology
MECHANISM OF VASCULAR ENDOTHELIAL GROWTH FACTOR BLOCKADE INDUCED MYELOSUPPRESSION IN LUNG CANCER PATIENTS TREATED WITH ANTI-VEGF THERAPY

Ildiko Csiki, MD, PhD, Sergey Novitsky, PhD, Mikhail Dikov, Phd, Alan Sandler, MD, David H. Johnson, MD, David P. Carbone, MD, PhD

Objectives
Lung cancer remains the number one cause of cancer death worldwide. Recently, the bevacizumab, carboplatin and paclitaxel (BCP) regimen was FDA approved in patients with non-squamous-cell carcinoma of the lung as a phase III study demonstrated that the addition of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), to standard chemotherapy improved survival and response rate. Along with these findings increased toxic effects, including febrile neutropenia, were noted with the addition of bevacizumab. The purpose of the study is to elucidate the mechanism of combination chemotherapy and bevacizumab induced myelosuppression and to examine the role of VEGF and its receptors in the proliferation of hematopoietic progenitor cells (HPCs). As VEGF receptors play important role in hematopoietic recovery after myelosuppression, we hypothesized that the combination of chemotherapy and anti-VEGF receptor treatment causes delayed hematopoietic recovery and neutropenia in patients.

Methods/Results
Through a retrospective analysis of patients receiving bevacizumab in combination with different chemotherapeutic agents for various cancers compared to matched patients receiving chemotherapy alone, we observed that bevacizumab in combination with chemotherapy significantly delays repopulation of white blood cells (WBC) including the neutrophils. Furthermore, we examined the combination effect of myeloablative agent and VEGF receptor tyrosine kinase inhibitors (VEGFR TKI) on the proliferation of HPCs in-vivo and found that wild-type mice treated with chemotherapy and VEGFR TKI as well as knock-out mice for VEGF receptor treated with chemotherapy had significantly delayed repopulation of WBC and impaired proliferation of HPCs. When present, VEGF increases the cell cycling of bone marrow cells and the proportion of HPCs in the bone marrow. However, interference with VEGF signaling delays WBC recovery and repopulation of bone marrow in mice. Furthermore, inhibition of VEGFR TKI and blockade of VEGF receptor signaling by anti-VEGF or anti-receptor reagents decreases proliferation of HPCs.

Conclusions
These results aid in our understanding of the mechanism of increased bone marrow toxicity observed clinically when using the BCP regimen in lung cancer patients as well as further our understanding of the role of VEGF and its receptors in angiogenesis and hematopoiesis.
INHIBITION OF GSK3β ENHANCES REPAIR OF RADIATION-INDUCED DNA DOUBLE STRAND BREAKS IN HIPPOCAMPAL NEURONS

Eddy S. Yang, MD, PhD, Somaira Nowsheen, MS, Dennis E. Hallahan, MD, and Fen Xia, MD, PhD. Dept of Radiation Oncology, Vanderbilt University School of Medicine

Purpose/Objective(s)
Long-term neurological deficiencies resulting from cranial radiation-induced hippocampal cytotoxicity presents a formidable challenge in the treatment of primary and metastatic brain cancers, especially in young children. We have previously shown that lithium protects hippocampal neurons from radiation-induced apoptosis and improves neurocognitive function in treated mice. However, this protective effect requires a 7-day prophylaxis prior to initiation of radiation. Additionally, lithium is non-specific and has a narrow therapeutic window. These factors may render lithium not feasible for use as a neuroprotector in patients with brain tumors. We recently reported that as little as 4 hours of specific inhibition of GSK3β, a target of lithium, can similarly protect irradiated neurons and improve cognitive function in irradiated mice. In this study, we demonstrate a novel role of DNA DSB repair in protection of irradiated mouse hippocampal neurons but not mouse glioma cancer cells through GSK3β inhibition.

Materials/Methods
Neutral comet assay kinetics to detect the efficiency of DSB repair were performed on irradiated HT22 hippocampal neurons or GL261 glioma cancer cells with or without GSK3β inhibition. % of cells with γ-H2AX foci (indicative of DNA double strand breaks) was assessed via immunohistochemistry. Rejoining of a linearized GFP plasmid in vehicle or GSK3β inhibitor treated cells was assessed via flow cytometry.

Results
Inhibition of GSK3β in irradiated mouse HT-22 hippocampal neurons accelerates DSB repair efficiency as assessed by the neutral comet assay. This coincides with a 2.5 fold increase in DNA end-rejoining activity in hippocampal neurons. An effect on DSB repair is validated with a marked reduction (from 75% to 25%) of cells with persistent radiation-induced γ-H2AX foci, robust in situ markers of DSBs. On the contrary, none of these findings are evident in the mouse glioma cancer cell line GL261.

Conclusions
Given lithium’s requirement for a 7 day prophylaxis, its narrow therapeutic window, and its lack of specificity, the use of GSK3β inhibitors as neuroprotectors provide clear advantages over lithium. Our results strongly support the hypothesis that inhibition of GSK3β protects hippocampal neurons but not glioma cancer cells by promoting DSB repair. This will not only link GSK3β signaling to DNA repair pathways but also generate novel targets for the development of neuroprotective drugs for use during whole brain radiation. Furthermore, these findings warrant future clinical investigations of neuroprotection with GSK3β inhibitors during cranial irradiation, especially in the pediatric population.
PROTEASE-ACTIVATED RECEPTOR (PAR-1) AGONIST PEPTIDE VASOCONSTRICTS CANINE EPICARDIAL CORONARY ARTERIES IN VIVO

Kasasbeh ES, Phillips SA, Liu Q, Krueger JG, Cleator JH

Objective(s)
Activation of PAR-1 in healthy human subjects causes endothelial dependent forearm arterial vasodilatation. In vitro studies in canine coronary artery rings have either shown vasodilatation or vasoconstriction. The in-vivo effects of PAR-1 activation on coronary vascular tone in any species are unknown. Therefore, we designed a non-survival canine study aimed at assessing the effects of PAR-1 agonist peptide on the epicardial coronary arteries in an in-vivo canine model.

Methods
PAR-1 agonist peptide was continuously infused into coronary arteries, and vessel diameter, mean arterial pressure and coronary velocity were measured (n = 7).

Results
Adenosine (endothelium-dependent) caused a marked increase in Coronary Blood Flow (CBF) and concomitant decrease in coronary vascular resistance (CVR). While acetylcholine (endothelium-independent) increased CBF and decreased in CVR in young healthy dogs (n = 3), in a subgroup of aging dogs (n = 4) decreased CBF and increased CVR suggesting endothelial dysfunction. There was an incremental dose response of increasingly higher doses of PAR-1 agonist peptide to decrease coronary diameter (~40% decrease in the proximal segment and a 60% decrease in the distal segment) in both subgroups of dogs. This corresponded to a reduction in CBF (~ 4 fold reduction in the proximal segment and a 22 fold reduction in the distal segment) at the highest dose of PAR-1 agonist peptide and an increase in CVR. There was no significant difference between the subgroups of dogs with PAR-1 agonist peptide suggesting that PAR-1 causes endothelial-independent vasoconstriction.

Conclusions
In conclusion, in vivo PAR-1 agonist peptide vasoconstricts canine coronary arteries and markedly reduces CBF and increases CVR. As PAR-1 antagonists become more clinically available, our data suggests that PAR-1 antagonism may be useful to treat the “no-reflow phenomenon” after percutaneous coronary intervention.
IMPACT OF CONDITIONING REGIMEN IN ALLOGENEIC HEMATOPOETIC STEM CELL TRANSPLANT FOR CHILDREN WITH AML BEYOND FIRST COMPLETE REMISSION: A PEDIATRIC BLOOD AND MARROW TRANSPLANT CONSORTIUM (PBMTC) STUDY

India Y Sisler MD, Tatsuki Koyama PhD, Elizabeth Koehler MS, Jennifer A Domm MD, Robin Ryan MPH, John E Levine MD, Michael A Pulsipher MD, Paul R Haut MD, Kirk R Schultz MD, Douglas S Taylor MD, Haydar A Frangoul MD

Objectives
The role of total body irradiation (TBI)-based conditioning regimens for pediatric patients with acute myeloid leukemia (AML) beyond first complete remission (CR) is controversial. Because the long term morbidity of busulfan-based regimens appears to be lower, determining efficacy is critical.

Methods
We retrospectively evaluated 151 pediatric patients with AML beyond first CR using data provided by the Pediatric Blood and Marrow Transplant Consortium. Outcomes were compared between the children receiving TBI-based (n=90) or busulfan-based (n=61) conditioning regimens.

Results
There were no differences between patients receiving TBI-based or busulfan-based conditioning regimens with respect to age, sex, duration of first CR (CR1), time from most recent remission to transplant, or donor source. Transplant related mortality (TRM) was not significantly different between the TBI and busulfan groups (25% vs. 16% respectively, p=0.29). The probability of relapse at 2 years was not different between the two groups (26% for TBI-based and 27% for Bu-based, p=0.93). There was no difference in event free survival (p=0.29) or overall survival (p=0.11) between the 2 groups. These findings were supported by a multivariable analysis, where TBI was not associated with improved EFS (HR=1.17, 0.66 to 2.10, p=0.58) or OS (HR=1.42, 0.76 to 2.64, p=0.27). Shorter first CR, longer time from second remission to transplant and receiving HLA mismatched transplant adversely affected EFS and OS in this cohort.

Conclusions
Our study provides no evidence of an advantage to using TBI in children with AML beyond first CR. Busulfan-based preparative regimens may be used preferentially due to the lower long-term morbidity for children in this setting.
PARENTAL KNOWLEDGE AND USE OF PREVENTIVE ASTHMA CARE MEASURES

Jamie N Deis, MD, David M Spiro, MD, MPH, Cathy A Jenkins, MS, Tamara L Buckles, MD, and Donald H Arnold, MD, MPH

Objective
Most asthma exacerbations are preventable, yet asthma is the most frequent reason for hospitalization of children in North America. Parents of children who visit the pediatric emergency department (PED) for asthma exacerbations may not receive adequate instruction in preventive asthma care. Our primary objective was to assess parental knowledge and use of preventive asthma care measures in children with asthma exacerbations. Our secondary objective was to identify variables that predict adherence to preventive care measures.

Methods
We administered a 38-item questionnaire to parents of children with asthma exacerbations aged 2 to 18 years who presented to two, urban PEDs in the southeast and northwest US. Descriptive statistics were calculated to assess parental knowledge of preventive care. Multivariable logistic regression was used to identify variables associated with adherence to preventive care.

Results
A total of 188 questionnaires were completed. Mean age of the children was 7.5 years (range 2-18), 49% were African American, 30% had an action plan, and 51% received a flu vaccine during the most recent season. Overall, 66% of the children had persistent asthma by NIH criteria. Of these, 25% had a peak flow meter, and 45% received daily inhaled corticosteroids (ICS). When parents were asked how an ICS medicine worked, 30% responded “immediately opens the airway”, and 26% responded “I do not know.” Daily use of ICS in these children was significantly associated with parent education level beyond high school (OR=3.12; 95% CI: 1.27, 7.66; P=0.013). The caregiver’s perception of his/her ability to provide care during an asthma exacerbation was significantly associated with receipt of an action plan in a multivariable proportional odds model (OR=3.67; 95% CI: 1.85, 7.29; P=0.0002).

Conclusions
Parents of children with persistent asthma presenting to urban tertiary care PEDs with asthma exacerbations frequently have inadequate understanding of appropriate ICS use, and many of their children lack important asthma self-management tools. Parents who receive a written action plan are more confident in their ability to provide care for their child during an asthma exacerbation.
NOREPINEPHRINE TRANSPORTER POLYMORPHISMS AFFECT BLOOD PRESSURE RESPONSE TO EXERCISE

Utkarsh Kohli, M.D., Maureen K. Hahn, Ph.D., Brett A. English, Ph.D., Mordechai Muszkat, M.D., Gbenga G. Sofowora M.D., Randy D. Blakely, Ph.D., C. Michael Stein, M.D., Daniel Kurnik, M.D.

Objectives
The norepinephrine transporter (NET) mediates re-uptake of norepinephrine at noradrenergic synapses. NET-deficient transgenic mice have elevated blood pressure, heart rate, and catecholamines. A rare NET variant elevates catecholamines in postural tachycardia syndrome patients, but the in vivo effects of common NET variants are largely unknown. We hypothesized that two common NET polymorphisms (T-182C and A-3081T) affect heart rate, blood pressure, and plasma catecholamines.

Methods
We studied cardiovascular responses at rest and during exercise at increasing workloads (25, 50 and 75 W for 2 minutes each) in 145 healthy subjects (82 females, 83 Caucasians and 62 African-Americans [AA]). Plasma catecholamines were measured at rest and after exercise. We used multiple linear regression to analyze the effect of NET variants on cardiovascular measures after adjusting for potential confounders (age, sex, race, exercise score, and pre-exercise value of the measure).

Results
44% (n=61, 22 AA) and 58.9 % (n=83, 44 AA) of subjects carried at least one NET T-182C and A-3081T minor allele, respectively. Systolic blood pressure (SBP) (Table) and SBP area-under-the-curve (AUC) during exercise (P=0.003 and 0.009) were higher in carriers of NET minor alleles, and diastolic BP also tended to be higher (Table); resting BP measurements did not differ. NET genotypes were not associated with plasma norepinephrine concentrations or heart rate at rest or during exercise.

Conclusions
The presence of the common -182C or -3081T NET alleles is associated with greater blood pressure response to exercise.
BASIC SCIENCE RESEARCH ABSTRACTS

(alphabetically by presenter’s last name)
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<td>Sachin Patel, MD, PhD</td>
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<td>John Gary Phillips, BS</td>
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<td>Kasra Attaran Rezaei, MD</td>
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<td>David Yu, MD, PhD</td>
<td>Resident, Radiation Oncology</td>
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ACHIEVING SYNAPTICALLY RELEVANT PULSES OF NEUROTRANSMITTER USING PDMS MICROFLUIDICS


Objectives
Fast synaptic transmission is mediated by the transient activation of post-synaptic ligand-gated ion channels (LGICs) following release of neurotransmitter from pre-synaptic vesicles. Increasing evidence suggests that the concentration of neurotransmitter in the synaptic cleft rises extremely rapidly before being cleared by diffusion and reuptake, with post-synaptic LGICs being exposed for a total of only 300-600 µs. Despite the fundamental importance of this process to proper functioning of the nervous system, reproducing the neurotransmitter transient in vitro has not been technically feasible.

Methods
To achieve synaptically relevant neurotransmitter pulses, we took a microfluidic approach. Drug application devices were fabricated using photolithography and replica molding from polydimethylsiloxane (PDMS), an inexpensive, durable, and inert polymer.

Results
By translating ultra-thin fluid streams (~10 µm) generated by these devices with a stepper motor, the microfluidic environment surrounding cells could be switched to one containing neurotransmitter in <100 µs. This neurotransmitter pulse could then be terminated within 400 µs. When applied to recombinant GABA_A receptors, members of the Cys-loop family of LGICs, currents evoked by these ultra-brief GABA pulses closely resembled hippocampal inhibitory post-synaptic currents (IPSCs) and had kinetic properties that differed from those evoked by conventional, longer pulses (i.e., 1-10 ms), including decreased peak amplitudes, accelerated deactivation time courses, and less sensitivity to repetitive stimulation.

Conclusions
Failure to activate LGICs in vitro with synaptically relevant pulses of neurotransmitter can markedly alter current kinetics. This novel experimental approach to solution switching should therefore improve our understanding of the role played by different receptor isoforms, allosteric modulators, and disease-causing mutations in synaptic physiology.
A NON-ELECTROGENIC ROLE FOR VOLTAGE-GATED SODIUM CHANNELS IN EARLY CARDIogenesis: A DEVELOPMENTAL MECHANISM UNDERLYING SODIUM CHANNEL-ASSOCIATED CARDIOMYOPATHY?

Sameer S. Chopra, Ph.D., Hiroshi Watanabe, M.D., Ph.D., Dina M. Stroud, Ph.D., Tao Yang, Ph.D., Tao P. Zhong, Ph.D., Dan M. Roden, M.D.

Objectives
Voltage-gated sodium channels initiate action potentials in excitable tissues. In the heart, mutations in SCN5A underlie multiple heritable arrhythmia syndromes. However, recent data also implicate SCN5A mutations in structural heart disease. The mechanism by which sodium channel dysfunction contributes to cardiomyopathy is unknown.

Methods
Antisense and pharmacology were used to study the role of cardiac sodium channels in zebrafish embryos.

Results
Two distinct zebrafish SCN5A homologs were identified, scn5aa and scn5ab. Cloning and heterologous expression of each ~6kb zebrafish cDNA in CHO cells reconstituted typical voltage-gated sodium currents. By whole mount in situ hybridization, scn5aa and scn5ab transcripts were detected at the margin of the late blastula, in mesoderm, and subsequently in the embryonic myocardium. Rather than causing arrhythmia, antisense knockdown of either channel resulted in anomalies of cardiac development including chamber malformation, perturbed looping, and decreased numbers of embryonic cardiomyocytes. In the early heart-forming region of anterior lateral mesoderm, antisense-treated embryos displayed reduced expression of the myocardial precursor genes nkx2.5, gata4, and hand2, indicating that scn5aa and scn5ab are required for cardiac specification. These deficiencies did not result from perturbed membrane electrophysiology, as pharmacological modulators of sodium current failed to phenocopy channel knockdown. At later stages, sodium current was similarly dispensable for cardiac differentiation and beating of the embryonic heart. Analysis of mosaic embryos revealed that sodium channels act non-cell-autonomously at early stages to regulate cardiac cell fate specification and autonomously at later stages to permit the proliferative growth of differentiated embryonic cardiomyocytes.

Conclusions
Voltage-gated sodium channels have evolved dual roles in the vertebrate heart: in addition to regulating the electrophysiology of the mature myocardium, they perform previously unrecognized, non-electrogenic functions during cardiac development. Our findings thus suggest a developmental mechanism for how mutations in a single ion channel gene may underlie the seemingly divergent phenotypes of arrhythmia and cardiomyopathy.
TUMOR SUPPRESSOR EFFECT OF SMAD4 EXPRESSION IN COLON CANCER

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Objectives
Epithelial to mesenchymal transition (EMT) has been described in the progression of colon carcinoma (CRC). The Adenomatous Polyposis Coli (APC) protein is considered a gatekeeper of carcinogenesis in CRC. Smad4 functions as the central mediator in TGF-β signaling, and mutations in Smad4, implicated in 20-30% of CRC, are associated with later stages of EMT. The mechanism of Smad4 maintaining an epithelial phenotype without functional APC is unknown.

Elucidate a mechanism by which Smad4 expression induces an epithelial phenotype in transformed CRC cells.

Methods
APC mutant, Smad4-expressing SW480 colon cells were engineered with a pCMV script expression vector (SW480Smad4 / SW480controls). Immunodetection for E-cadherin, β-catenin and vimentin was performed. Matrigel invasion assays were conducted comparing SW480controls and SW480Smad4 cells while controlling for proliferation. Bilateral flank injections were administered by injecting SW480controls and SW480Smad4 cells into nude mice (n=16). Tumors were harvested 28 days after injection, and tumor volume was determined ex vivo.

Results
E-cadherin co-localized with β-catenin to the cell membrane in SW480Smad4 cells by immuno-fluorescence. E-cadherin was diffusely localized to the cytoplasm of the more spindly SW480control cells, and β-catenin was both cytoplasmic and nuclear. Immunoblot showed vimentin to be down-regulated in SW480Smad4 versus SW480controls cells. SW480Smad4 cells are significantly less invasive through matrigel than SW480control cells (p<0.001). SW480Smad4 cells are significantly less tumorigenic in flank injections than SW480controls cells (p<0.03).

Conclusions
Smad4 loss in APC-mutated SW480 cells promotes EMT as evidenced by mislocalization of E-cadherin and β-catenin. Furthermore, Smad4 expression in SW480 cells is associated with reduced vimentin levels, in vitro invasion, and in vivo tumorigenesis.
NOVEL METHOD TO GENERATE ANTI-HIV HUMAN MONOCLONAL ANTIBODIES REVEALS EXTENSIVELY MUTATED ANTIBODIES

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Objectives
To improve the understanding of how native antibodies (Abs) bind and neutralize HIV to assist in future rational vaccine design.

Methods
Over-expression of Gag, Env, and Vpr-GFP proteins creates fluorescently labeled HIV virus-like-particles (VLPs). These VLPs can specifically label HIV-infected subject B cells. Using high-speed flow cytometric sorting, CD19+ (a pan B-cell marker) and GFP double-positive cells (VLP-labeled) are sorted as single cells into 96-well plates with appropriate cytokines and CD40L+ feeder cells. ELISA screening was used to identify Ab producing clones of interest and RT-PCR of the clones RNA was used to clone Ab heavy and light chain variable gene segments.

Results
On ELISA screening, the majority of the screened supernatant Abs bind to trimeric envelope (VLP binding) rather than monomeric gp120. Clone 2C6 is an example of such a clone. Sequence analysis of 2C6 revealed homology to a known anti-HIV monoclonal Ab 47e, but 2C6 is more heavily mutated. Heavy and light chains of 2C6 were cloned into a Fab expression vector and the 2C6 Fab similarly preferentially bound VLP and not the monomer gp120, recapitulating supernatant binding, and implying a conformational epitope restriction of the 2C6 Ab compared to 47e. On comparison to other known Abs including those against HIV, this collection of 50 novel anti-HIV Abs are some of the most highly mutated Abs described.

Conclusions
This collection of Abs are highly mutated and appear to bind quaternary structures on trimeric envelope protein. Abs similar to these may be necessary to form broadly neutralizing antibodies to HIV and may be an important goal of future vaccination regimens.
SODIUM CHLORIDE INDUCES BROAD SPECTRUM RESISTANCE TO ANTI-
BIOTICS IN ACINETOBACTER BAUMANNII

Indriati Hood, Anna Jacobs, Paul Dunman, and Eric Skaar

Objectives
Acinetobacter baumannii has recently emerged as an important cause of nosocomial infections. Extensive antimicrobial resistance has been described clinically, yet the molecular determinants of resistance and associated regulatory mechanisms are poorly defined. The objective of this work is to identify signals encountered in the hospital setting, which alter the resistance phenotype of A. baumannii. Current work is aimed at defining the molecular determinants responsible for translating these environmental signals into an adaptive response.

Methods
A. baumannii was challenged with sub-lethal concentrations of antibiotics in low or high NaCl media to determine the effect of NaCl on antibiotic resistance. Microarray analyses were employed to define the transcriptional response of A. baumannii to NaCl. To identify specific genes mediating NaCl-induced antibiotic resistance a transposon insertion library was generated and screened for mutants that failed to show increased resistance to antibiotics in the presence of NaCl.

Results
A. baumannii cultured in 50mM-300mM NaCl exhibited increased resistance to aminoglycosides, carbapenems, quinolones and colistin. Inhibition of transcription abolished NaCl-induced resistance demonstrating that this response is transcriptionally-dependent. The global transcriptional response to NaCl determined by microarray analyses suggests a role for efflux in mediating resistance to antibiotics. Specifically, 14 transporters with putative roles in antibiotic efflux were significantly up-regulated in response to NaCl. Mutants that fail to show increased resistance to antibiotics in response to NaCl have been identified through a transposon insertion library screen. The genes disrupted in these mutants include a putative two-component system sensor kinase, and genes with predicted roles in protection against oxidative stress and maintenance of membrane structure.

Conclusions
We have identified NaCl as an important signal that induces resistance to multiple antibiotics in A. baumannii. Future work will focus on exploiting mutants identified in the transposon screen to define the molecular mechanisms governing NaCl-induced antibiotic resistance.
THE AURORA KINASE A POLYMORPHISM rs1468055 IS ASSOCIATED WITH OVERALL SURVIVAL IN PROSTATE CANCER PATIENTS

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Background
The association between functional AURKA SNPs and malignant tumor phenotypes from previous studies hint at their prognostic implications in cancer therapy. Interestingly, recent findings point to the importance of introns in altering the transcriptional activation of pro-apoptotic or cell cycle genes such as Bax and Cyclin D3. We have thus selected the four 5’ intronic haplotype-tagging SNPs (htSNPs) in the AURKA gene and examined its influence on clinical outcomes in 212 patients status post radical prostatectomy as primary treatment.

Methods
Haplotype-tagging SNPs (htSNP) were selected using the ABI SNP Browser to cover SNPs with an r² of 0.90 or greater in the AURKA gene with a minor allele frequency (MAF) of at least 0.25. Univariate and multivariate statistical analyses were then carried out to examine the clinicopathologic outcomes associations. In addition, an in silico prediction method with the MatInspector software was utilized to detect changes in transcription factor binding with the SNP of statistical significance.

Results
Multivariate analysis yielded a statistically significant correlation between the A allele of rs1468055 (C>A) of the AURKA gene and decreased overall survival. The SNP also exerted a risk-enhancing effect independently of other known prognostic factors such as PSA, Gleason grade, and surgical margin.

Conclusion
To our knowledge, SNP rs1468055 is the first intronic genetic marker found to alter the survival outcome of prostate cancer patients. The current study underscores the potential application of nonfunctional AURKA SNPs in predicting outcomes in prostate cancer and studying the molecular mechanisms behind tumor progression.
EGFR IS REQUIRED FOR COX-2 INDUCTION BY LPS IN INTESTINAL EPITHELIAL CELLS

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Background
Necrotizing Enterocolitis (NEC) is a feared complication in preterm infants characterized by an exaggerated inflammatory response to pathogenic flora leading to bowel necrosis and often death. Bacterial lipopolysaccharide (LPS) mediates inflammation and is a potentially key molecule in NEC pathology. Conversely, induction of cyclooxygenase-2 (COX-2) in response to LPS may promote intestinal barrier function through regulation of intestinal cell survival, proliferation, and migration, and may thus help protect from NEC. LPS induces p38 MAPK-dependant expression of COX-2 through a yet unknown pathway. Epidermal Growth Factor Receptor (EGFR) has been described as important in prevention of experimental NEC and may be critical for LPS-stimulated COX-2 production.

Objective
This study tests the hypothesis that EGFR is required for LPS induction of COX-2 expression.

Method
We evaluated COX-2 expression in IEC-6 cells by Western blot. We used AG1478, an EGFR kinase inhibitor, to investigate the EGFR requirement in LPS-induced p38 activation and COX-2 expression. We determined whether LPS transactivates EGFR by investigating EGFR phosphorylation by Western blot with phospho-specific antibodies.

Results
LPS treatment of IEC-6 cells induced EGFR and p38 phosphorylation, and COX-2 expression. LPS and EGF in combination stimulated higher COX-2 expression than treatment with LPS alone but not EGF alone, indicating a common pathway. Pretreatment with AG1478 blocked both p38 phosphorylation and COX-2 induction in LPS-stimulated IEC-6 cells.

Conclusion
EGFR is a key molecule for LPS induced COX-2 expression in intestinal epithelial cells, which may be one mechanism for its role in NEC prevention.
HYPOXIA IN KIDNEYS OF b-TALASSEMIC MICE IS ASSOCIATED WITH PROFIBROTIC TRANSCRIPTIONAL RESPONSE IN THE ABSENCE OF TUBULOINTERSTITIAL INJURY

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Objectives
Recent data suggest that hypoxia may represent an early and potentially initiating event in the development and progression of renal disease. Hypoxic induction of profibrotic mediators has been demonstrated in multiple animal models of chronic kidney disease. However, in the absence of renal scarring, the hypoxia-driven profibrotic transcriptional activation remains undefined. In order to address this issue we used b-thalassemia as an in vivo model of chronic hypoxia.

Methods
Affected mice, at 2 month of age (th3/th3), which are known to have very low Hgb levels (average 4 g/dL), were compared to heterozygous mice (th3/+) and wild type littermates (+/+). Transcriptional responses were assessed by microarrays and RT-PCR, whereas Hif-1 and Hif-2 protein levels were measured by Western-blot.

Results
Western-blot revealed Hif-1 and Hif-2 stabilization in nuclear extracts form kidney homogenates of th3/th3 mice. Microarray analysis of the kidney homogenates showed up-regulation of many known hypoxia-regulated genes. RT-PCR confirmed the microarray data for all the genes tested. Some of the genes found to be significantly up-regulated in kidneys from th3/th3 mice compared to wild type ones were; Ho1, Ca9, Lcn2, Adamts4, Col6a1 and LoxL2, which demonstrated a 3.3, 5.5, 6.4, 5.2, 5.2 and 2.0- fold induction, respectively. H&E and PAS staining of kidney sections did not reveal any overt signs of tubulointerstitial injury despite the presence of profibrotic molecular signatures.

Conclusions
In summary our data suggest that the profibrotic transcriptional cascade associated with hypoxia is present in kidneys from b-thalassemic mice at 2 months of age, not sufficient though in promoting renal fibrogenesis. Additional molecular and pathophysiologic events such as altered hemodynamics, TGFβ signaling, reactive oxygen species and inflammation are potentially required in concert with hypoxia, in order to set a healthy kidney in motion to scar formation.
MULTIPLE BACTERIA INDUCE NATURAL KILLER T CELL HYPORESPONSIVENESS IN VIVO

Sungjune Kim, Saif Lalani, Vrajesh V Parekh, Tiffaney L Vincent, Lan Wu, and Luc Van Kaer

Objectives
To delineate the impact of pathogenic bacteria on host immune system

Methods
Mice were infected with various bacteria and analyzed for iNKT cell functions at different time points after infection. Further mechanistic studies were performed using IL-12 deficient mice, and use of TLR ligands. Effect on therapeutic activity of iNKT cells were also analyzed using various models.

Results
Invariant natural killer T cells (iNKT) cells are innate-like lymphocytes that recognize glycolipid antigens in the context of the MHC class I–like antigen-presenting molecule CD1d. In response to invading bacteria, iNKT cells secrete a copious amount of various cytokines activating both the innate and adaptive immune system. Interestingly, we have found that bacteria also impact iNKT cell phenotype and functions. A careful analysis of this pathogen-host interaction between bacteria and invariant NKT (iNKT) cells revealed that primary stimulation of iNKT cells by multiple bacteria, or bacterial products such as LPS and flagellin, render iNKT cells unresponsive during the subsequent activation with α-GalCer. Infection studies with IL-12 deficient mice revealed requirement for IL-12 expression for bacteria-induced iNKT cell hyporesponsiveness. Also, iNKT cell hyporesponsiveness was associated with changes in the surface phenotype of these cells, reduced severity of concanavalin A–induced hepatitis in which iNKT cells have been shown to exhibit pathogenic roles. iNKT cell hyporesponsiveness also resulted in the alterations in the therapeutic activities of α-GalCer.

Conclusions
Based on these results, we conclude that certain bacterial infection or vaccines may negatively impact iNKT cell functions which are currently being exploited for their anti-tumor activity, adjuvant activity, as well as their immunomodulatory functions in various autoimmune diseases. These findings may have important implications for the development of iNKT cell–based therapies.
THE CONTRIBUTION OF HEME-IRON ACQUISITION TO STAPHYLOCOCCUS AUREUS PNEUMONIA

William Jeffrey Mason and Eric P. Skaar

Objectives

*Staphylococcus aureus* is a common cause of hospital acquired pneumonia and community associated methicillin resistant *S. aureus* (CA-MRSA) infections are now a global problem. Virtually all vertebrate pathogens require iron for metabolic activity and growth. How *S. aureus* acquires iron in the lung is not known. The iron regulated surface determinant system (Isd) in *S. aureus* consists of a series of surface proteins (IsdA, IsdB, and IsdH), membrane bound proteins (IsdC, IsdD, IsdE, IsdF) and cytoplasmic proteins (IsdG and IsdI) responsible for the acquisition of iron from vertebrate hemoglobin. We have developed a murine model of staphylococcal pneumonia to test the hypothesis that heme-iron acquisition through the Isd system is required for virulence.

Methods

Mice were intranasally inoculated with ~$1.0\times10^8$ colony forming units (CFU) of *S. aureus*. Lungs from mice infected with wild type *S. aureus* or strains deficient in *isdB* and *isdH* ($\Delta$isdBH) or *HtsA* and *isdE* ($\Delta$HtsA/IsdE) were harvested at 24 hours. Histology, radiographic appearance by computed tomography (CT), percent mortality and bacterial burden were evaluated.

Results

Infection with *S. aureus* $\Delta$isdBH and $\Delta$HtsA/IsdE did not result in a statistically significant difference in mortality or bacterial burden as compared to controls. Histological analyses of explanted lung tissue revealed the presence of pneumonia in wild type, $\Delta$isdBH, and $\Delta$HtsA/IsdE infected animals, but no differences were detected in overall histology. CT imaging of infected mice also did not reveal an appreciable difference between the various strains when compared to wild type, but did correlate with histologic findings of pneumonia.

Conclusions

The development of staphylococcal pneumonia in this murine model is not dependent on the hemoglobin receptors, IsdB and IsdH, or the cell wall/membrane anchored proteins, HtsA and IsdE. In addition, CT imaging of murine lungs is an attractive alternative to histologic analysis for the confirmation and staging of pneumonia.
AZD1152, AN AURORA KINASE B INHIBITOR, INCREASES G2/M AND POLYPLOID CELLS AND INCREASES RADIOSENSITIZATION IN TWO PROSTATE CANCER CELL LINES

Lauren Rhea Mitchell, Prapaporn Kopsombut, Bo Lu

Objectives
Aurora kinase B (AURKB) is critical to mitosis, aiding in chromosome condensation via phosphorylation of histone 3 (p-H3). AZD1152 is a selective inhibitor of AURKB, resulting in cell cycle arrest and formation of polyploid cells. In this study, we investigated the effects of AURKB inhibition by AZD1152 + radiation in PC3 and DU145 prostate cancer cell lines.

Methods
PC3 and DU145 cells were treated with various doses of AZD1152 for various time points and p-H3 levels were examined by western blot. Cell cycle phases were analyzed after incubation with DNase-free RNase A followed by propidium iodide. Cells were treated with DMSO or 60nM AZD1152 for 48 hours followed by administration of 0 or 5Gy radiation with a $^{137}$Cs irradiator. DNA damage was determined based on the appearance of 40 or more fluorescent foci. Clonogenic assay was used to determine radiosensitivity.

Results
Levels of p-H3 were found to decrease with increasing AZD1152 doses and duration of treatment in both cell lines. Analysis of cell cycle indicated that increasing concentrations of AZD1152 and treatment duration resulted in a decrease of G0/G1 cells and an increase in G2/M and polyploid cells. Based on these data, we elected to investigate effects of 60nM AZD1152 for 48hr + radiation. A DNA damage assay indicated that 30min following 5Gy, more AZD1152-treated PC3 cells sustained DNA damage than irradiated controls (100% vs. 68.00%, p=0.035). Significantly, when assessed 6hr post-radiation, DNA damage was still higher in treated cells (85.33% vs. 15.33%, p=0.002). Comparison of treated DU145 cells to irradiated controls yielded similar results (30min: 100% vs. 69.33%, p=0.034; 6hr: 70.67% vs. 21.33%, p=0.012). Clonogenic assay revealed increased radiosensitivity following AZD1152.

Conclusions
Analysis of p-H3 levels and cell cycle arrest indicated that inhibition of AURKB resulted in an increase in G2/M and polyploid cells in PC3 and DU145 cell lines. This corresponded to an increase in sustained DNA damage following radiation and ultimately, radiosensitization. This study suggests that AURKB inhibition + radiation may be a promising approach in cancer therapy.
REPEATED HOMOTYPIC STRESS ELEVATES 2-AG LEVELS AND ENHANCES DEPOLARIZATION-INDUCED SUPPRESSION OF INHIBITION IN BASOLATERAL AMYGDALA

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Objectives
Stress is a major risk factor for development and exacerbation of neuropsychiatric illness. We have previously shown that repeated stress increases levels of the endocannabinoid 2-arachidonylglycerol (2-AG) in limbic brain regions or mice, and that blockade of cannabinoid type-1 receptors reverses habituated neuronal activation and active coping behaviors during restraint exposure. Based on these data we have suggested a role for endocannabinoid signaling in stress–response habituation.

Methods
We utilized mass spectrometry and whole cell patch clam electrophysiology to examine stress regulation of 2-AG signaling in the amygdala.

Results
Here we show that the 2-AG synthetic enzyme diacylglycerol lipase alpha is heterogeneously expressed in the amygdala and that levels of 2-AG are transiently increased in the basolateral amygdala in response to the 10th restraint stress exposure. Decreases in the 2-AG degradation product arachidonic acid were also observed, while 2-AG precursors were significantly elevated. In order to examine the synaptic correlates of these adaptations in 2-AG metabolism, we utilized whole-cell patch clamp recordings from BLA principle neurons to determine the effects of repeated stress on a form of endocannabinoid–mediated synaptic plasticity, depolarization-induced suppression of inhibition (DSI). DSI is mediated by 2-AG in the BLA, and its duration limited by eCB degradation. After 10 days of restraint stress, DSI duration, but not magnitude, was significantly enhanced.

Conclusions
These data indicate that exposure to repeated homotypic stress produces neuroadaptations that confer BLA neurons with an enhanced capacity to elevate 2-AG content and engage in 2-AG-mediated short-term retrograde synaptic signaling. We suggest stress-induced enhancement of endocannabinoid-mediated suppression of inhibitory transmission in the BLA could contribute to affective dysregulation associated with chronic stress. Pharmacological interventions aimed at reducing stress-induced endocannabinoid activation may represent novel approaches to the treatment of affective disorders.
TARGETED DRUG DELIVERY USING RECOMBINANT PEPTIDES

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Objectives
The goal of this study is to use ionizing radiation (XRT) to target the chemotherapeutic drug Taxol to tumors by conjugating them with phage selected recombinant peptides. Targeting drugs to tumors that respond to radiotherapy will enhance their biological effect and could reduce systemic toxicity.

Methods
We have shown (Z. Han, Nat. Med.) that biopanning of a phage-based peptide library in tumor bearing mice treated with XRT can identify peptides that recognize cancer response to therapy. We attached one such peptide, GIRLRG, to a polyester nanoparticle that contains Taxol (NP) in a controlled release system. Nude mice were implanted in the hindlimb with GL261 glioma cells or with MDA-231 breast cancer cells. The groups were untreated; NP-GIRLRG; NP-RILGGR; XRT; XRT+NP-GIRLRG; XRT+NP-RILGGR; and XRT+Systemic Taxol. Treatment was 10 mg/kg of NP and 3 Gy daily over 3 days. Spectroscopy analyses were performed to determine concentration of Taxol from in vitro cells and in vivo tumor and organ samples.

Results
XRT treatment of MDA/HUVEC and GL261/HUVEC co-cultures increased Taxol concentration compared to untreated co-cultures of the NP containing GIRLRG but not scrambled peptide. We found no preferential targeting of the NP-GIRLRG complex in XRT-treated cultures of MDA, GL261 and HUVEC alone. In vivo GL261 tumor tripling time was delayed 8 days by XRT+NP-GIRLRG but only 2 days with XRT or NP alone (P<0.05). MDA tumor tripling time was delayed 55 days by XRT+NP-GIRLRG but only 13-20 days by the 3 other radiation-treated groups (P<0.05). Spectroscopy showed no difference in Taxol levels of plasma, muscle, kidney and liver samples between synthetic control and targeted peptides (P<0.05).

Conclusions
Chemotherapeutic drugs like Taxol can be targeted with XRT by conjugating them with a nanoparticle/recombinant peptide complex. Targeting these therapeutic agents to tumors enhances the biological effect of Taxol with decreased levels in other organs. In vitro experiments indicate that tumor/tumor vasculature interaction is necessary for peptide binding, likely a result of a chemokine or a cytokine secreted by the tumor in response to therapy that activates the GIRLRG peptide’s receptor. Experiments to identify the receptor are underway that would allow for enhanced targeted drug delivery.
IDENTIFICATION OF NOVEL SMALL MOLECULES THAT REGULATE CARDIOMYOCYTE DEVELOPMENT

Eric Rellinger, Terri Ni, Charles Williams, Lauren Stephens, Jianyong Hu, Antonis Hatzopoulos, Tao P. Zhong

Objectives
Our primary goal was to identify and characterize small molecule modulators of cardiomyocyte development using a novel, in vivo cardiomyocyte generation assay in zebrafish. Active compounds may serve as leads for developing strategies to reconstitute cardiomyocyte populations following myocardial infarction.

Methods
We conducted a small molecule screen to identify compounds that modulate heart size using transgenic zebrafish embryos featuring EGFP expression in embryonic hearts. Active compounds were characterized in zebrafish to determine their mechanism of myocardial expansion, developmental period of efficacy, and target pathway. Parallel studies were conducted using murine embryoid bodies to assess whether compound activity was conserved in mammals.

Results
Three structurally-related compounds (Cardionogen A-C) potently increased zebrafish heart size in our screening assay. Cardionogen enlarges embryonic heart size via myocardial hyperplasia. These increases in cardiomyocyte populations are due to expansion of cardiac progenitor cell domains. Cardionogen acts in a biphasic manner, either promoting or inhibiting cardiogenesis depending on the stage of development. In both zebrafish embryos and mouse embryonic stem cells, treatment with Cardionogen after germ layer formation promotes cardiogenesis, whereas treatment before the formation of germ layers inhibits heart specification. This biphasic pattern of activity inversely resembles the role of Wnt/β-catenin signaling in cardiac development. Cardionogen-induced effects are antagonized by increasing Wnt/β-catenin signaling. We have also demonstrated that Cardionogen inhibits β-catenin/T cell factor (Tcf)-mediated transcription and can rescue specific heart phenotypes induced by increasing wnt8 expression during early or late development.

Conclusions
Cardionogen modulates cardiomyocyte development by opposing Wnt/β-catenin signaling. Given the roles of Wnt/β-catenin signaling in regeneration, stem cell formation and cancer progression, Cardionogen may have potential therapeutic benefits in both heart disease and cancer. Our findings demonstrate that developmental, phenotype-based chemical screens can identify compounds with cardiogenic activity and their underlying target pathways.
ZIP 2 EXPRESSION IN RPE CELLS

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Purpose
Although the Age-Related Eye Disease Study (AREDS) has shown that supplemental dietary zinc decreases the progression of age-related macular degeneration (AMD), little is understood about the molecular mechanisms of this effect. The purpose of this study is to explore how zinc protects by characterizing the zinc transporter proteins in human retinal pigment epithelial cells (RPE).

Methods
Human RPE cells were isolated from postmortem donor eyes. Pure cultures were obtained and RPE cells were incubated for 6 hours with various concentrations of zinc (5, 10, 50 and 100mmole) and 2 and 4mmole N,N,N,N-Tetrakis(2-Pyridylmethyl)ethylenediamine (TPEN) to induce zinc deficiency. The expressions of transporter proteins that mediate the uptake of zinc were analyzed by RT-PCR using gene-specific primers. Flow cytometry with FluoZn TM-3 was utilized to assess the intra-cellular zinc concentration.

Results
RT-PCR studies suggested that human RPE cells expressed Zip 2 as the predominant transporter. When the extracellular concentration of zinc was increased, the intracellular concentration increased as well, and was accompanied by an increase in the expression of Zip2. When TPEN was added to the culture medium, the intracellular zinc concentration diminished, and was accompanied by a decrease in Zip2 expression.

Conclusions
Zinc is an important trace element which is present in RPE cells and has been shown to protect the RPE against oxidative stress. The zinc transporter protein, Zip2, was identified as a predominantly expressed transporter in RPE cells and its expression appears to be regulated by the concentration of zinc. This mechanism of uptake should play a critical role in zinc protection of RPE cells from oxidative stress.(Supported by NIH grant EY 07892, Foundation Fight Blindness and Research Prevent Blindness, Inc.)
OBJECTIVES

Nearly 1% of live births are complicated by the presence of a congenital cardiovascular defect (AHA 2009), which are surgically repaired with the aid of cardiopulmonary bypass. Mitochondrial DNA deletions have been observed in adult populations undergoing CABG (Levitsky et al. 2003); however, the association between cardiopulmonary bypass and mitochondrial toxicity in children is unknown. Through this study, we aim to assess the effects of cardiopulmonary bypass on mitochondrial DNA copy number.

METHODS

Blood samples were collected from thirty children undergoing surgical repair of congenital heart defects. Blood was collected at the following times: before bypass was initiated, at 30 minutes on bypass, following cessation of bypass, two hours post bypass, six hours post bypass. Total genomic DNA was purified using the DNeasy Blood and Tissue Kit (Qiagen). Real-time PCR was used to determine mtDNA copy number using TaqMan assays (Applied Biosystems) with probes specific to mitochondrial gene ND5 normalized to the nuclear gene for RNAseP.

RESULTS

Mitochondrial DNA copy number declined progressively across all study time points (p<0.01), with the largest decline (46.3%) occurring between the pump30 and post-pump time points (p<0.001). We observed that the acyanotic physiologic subgroup had a significantly larger decline in mtDNA than the group with cyanotic physiology (p<0.01).

CONCLUSIONS

Cardiopulmonary bypass in children undergoing surgical correction of congenital heart anomalies leads to a significant decline in mtDNA. Loss is most drastic during bypass administration, which cannot be fully explained by loss of platelets as previously observed (Kirshbom et al. 2006). Further studies will look at more intensive markers and cell subsets.
VALPROIC ACID PROTECTS HIPPOCAMPAL NEURONS FROM RADIOTOXICITY IN VITRO AND IN VIVO

Kyle R Sweeney; Dennis E. Hallahan, MD; and Thotala Dinesh Kumar, Ph.D

Objectives
To demonstrate that Valproic Acid (VPA) increases survival and decreases radiation induced damage in irradiated hippocampal neurons.

Methods
Immortalized mouse hippocampal neurons (HT-22) were used for in vitro studies. Clonogenic survival assays were used to evaluate the role of VPA in cell survival. Apoptosis was measured by AnnexinV assays. Cell cycle analysis was performed by staining cells with PI. Protein changes were analyzed by subjecting the cell lysates to immunoblotting. Seven-day old C57BL6 pups were used to study apoptosis in vivo.

Results
Pretreatment of HT-22 cells with VPA for 24 hours resulted in accumulation of hyperacetylated histone H4 in a dose-dependent manner. Interestingly pretreatment of HT-22 cells also led to increased phosphorylation of GSK-3β at serine 9 (inactive form) and increased accumulation/stabilization of β-catenin. These results indicate that VPA inhibits not only HDAC, but also GSK-3β. Clonogenic survival assays showed that pretreatment of HT-22 with 0.6 mM VPA for 7 days before irradiation resulted in significantly increased cell survival as compared to cells treated with radiation alone. This phenomenon was not observed in glioblastoma cell lines D54 or DAOH. In animal models pups pretreated with 400mg/Kg of VPA for 7 days followed by 7 Gy radiation showed decreased pyknotic nuclei in the sub-granular region of hippocampus compared to animals treated with 7 Gy alone.

Conclusions
VA protects hippocampal neurons from radiation-induced damage in cell culture and animal models. This protection is specific to normal neuronal cells and does not extend to cancer cells. The molecular mechanism could involve inhibition of HDAC and GSK-3β. VA could be used as a novel therapy for the prevention of neurocognitive deficits resulting from cranial irradiation.
AGE-RELATED FIBROBLAST RESPONSES TO VOCAL FOLD INJURY

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Objectives
Age and injury related voice changes result from a disruption in the normal balance of the vocal fold extracellular matrix (ECM). Previous studies have revealed dense collagen deposition and reduced hyaluronan in the aged and scarred vocal fold. The change in cellular response to injury with aging is poorly understood. This study investigates gene expression of fibroblasts from young and aged rat vocal fold in response to vocal fold scarring.

Methods
Twelve 2-month old (young) and twelve 18-month old (aged) Sprague-Dawley rats were used in this study. Young and Aged rats were further divided into two groups (control and injury). Rats in the injury group received bilateral vocal fold injury and were euthanized two months after injury. Rats in the control group were painlessly sacrificed without vocal fold injury. Fibroblast cultures were established from harvested vocal fold specimens. Real-time PCR was used to quantify messenger RNA expression of hyaluronan synthase (HAS)-1, -2, -3 and matrix metalloproteinase (MMP)-2, -9 from second passage fibroblast cultures. Two-sample Wilcoxon Tests were used to investigate differences in gene expression between 2 and 18 month old rats and between control and injury.

Results
Fibroblasts from young injured rat vocal folds revealed increased HAS-2 (p=0.001), decreased HAS-3 (p=0.021), increased MMP-2 (p=0.048) and increased MMP-9 (p<0.001) in comparison to young control rat vocal folds. Fibroblasts from aged injured rat vocal folds revealed increased HAS-2 (p=0.048) and decreased HAS-3 (p=0.011) in comparison to aged control rat vocal folds.

Conclusions
Fibroblasts from young rat vocal folds showed changes in HAS and MMP expression after injury. Fibroblasts from aged rat vocal folds revealed changes only in HAS expression after injury. MMPs play an important role in maintaining tissue homeostasis and during wound healing. Results may provide evidence for decreased regenerative capacity after vocal fold injury with aging.
A LOSS OF FUNCTION GENETIC SCREEN IDENTIFIES CDK9 AS A NOVEL REPLICATION STRESS RESPONSE PROTEIN

David S. Yu*†, Runxiang Zhao†, and David Cortez†
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Vanderbilt University Medical School, Nashville TN

Objectives
The precise replication of the genome and the continuous surveillance of its integrity are essential for cell survival and the avoidance of various diseases, including cancer. The genome is constantly exposed to environmental and endogenous genotoxic insults. To cope with this challenge, the replication stress response (RSR) has evolved to coordinate diverse DNA repair and cell cycle checkpoint pathways. The objective of this study was to identify novel proteins involved in mediating the RSR.

Methods
We completed an unbiased loss of function genetic screen using a library of 27,976 siRNAs corresponding to four unique siRNA duplexes, targeting each of 6,994 unique human genes in U2OS human osteosarcoma cells to identify genes, which maintain viability following a replication challenge of hydroxyurea (HU) treatment. Candidate RSR genes were validated by secondary screens for cell cycle recovery after a challenge of HU and γH2AX phosphorylation in the absence of exogenous DNA damage following gene knockdown. Immunoprecipitation-western studies were completed to determine if a novel RSR protein, CDK9 interacts with components of the RSR. The localization of CDK9 in cells was determined by indirect immunofluorescence. CDK9-WT and CDK9-D167N, a kinase dead mutant, were tested in functional complementation assays. CDK9 was also tested for its ability to maintain the G2/M checkpoint following ionizing radiation (IR).

Results
We identified 14 high-confidence RSR genes, including the novel RSR gene, CDK9. Depletion of CDK9 causes HU hypersensitivity, impaired cell cycle recovery, and induction of γH2AX foci. CDK9 also interacts in a complex with a number of RSR proteins, including ATR/ATRIP, claspin, RPA70, and BRCA1 and localizes to ATRIP foci after replication stress. CDK9 knockdown impairs G2/M checkpoint maintenance after IR. Finally, the kinase function of CDK9 is essential for its activity in mediating cell cycle recovery.

Conclusions
CDK9 is a novel RSR protein which interacts with and localizes with components of the RSR. CDK9 is essential for mediating recovery after replication arrest and for G2/M checkpoint maintenance. The kinase function of CDK9 is essential for its RSR activities.
CLA INICAL SCIENCE RESEARCH

ABSTRACTS

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KIDNEY TRANSPLANT RECIPIENTS MAINTAIN PROTECTIVE TITER TO INACTIVATED INFLUENZA VACCINE

Kelly Birdwell MD, MSCI, Mine Ikizler MS, T. Alp Ikizler MD, Peter Wright MD

Objectives
To compare the maintenance of protective titer induced by influenza vaccination in kidney transplant recipients with controls.

Methods
Kidney transplant and healthy control subjects were recruited prior to the 2006-7 influenza season and given inactivated intramuscular influenza vaccine. Transplant subjects were on tacrolimus-based immunosuppression regimens +/- prednisone. Serum was collected pre-vaccination, one month post-vaccination, and the end of influenza season and tested for antibody responses against A/H1N1, A/H3N2, and B by hemagglutinin inhibition assay. Those who developed a protective titer of $\geq 1:32$ at one month were assessed for maintenance of titer at the end of season (N controls = 76, 84, 86 and N transplants = 26, 24, 31 for A/H1N1, A/H3N2, B, respectively). Primary outcome was proportion of subjects with less than a four-fold change in titer at the end of influenza season. Chi-square testing was used.

Results
Age was the same among groups with median 41 years. As expected, serum creatinine was different for the 2 groups (controls 0.9 mg/dL, transplant 1.4 mg/dL, p < 0.001). Maintenance of protective titer was similar and high for both groups for all 3 influenza types: A/H1N1, 80.3% controls and 80.8% transplants; A/H3N2, 58.3% controls and 70.8% transplants; B 73.3% controls and 80.6 transplants

Conclusions
Kidney transplant subjects who achieve protective titer to inactivated influenza vaccine maintain it for the duration of influenza season comparable with healthy controls.
HIGHLY-SENSITIVE C-REACTIVE PROTEIN (hsCRP) IS ASSOCIATED WITH BODY MASS INDEX (BMI) AND SERUM LIPIDS IN HIV-INFECTED PATIENTS WITH LOW CARDIOVASCULAR DISEASE (CVD) RISK AND VIROLOGIC SUPPRESSION ON ANTIRETROVIRAL THERAPY (ART)


Objectives
Metabolic abnormalities complicating ART may lead to increased CVD risk. hsCRP predicts CVD risk in the general population; less is known about its use in HIV-infection. Our objective was to assess relationships between hsCRP and metabolic parameters in HIV-infected patients on ART.

Methods
Data are from a prospective cohort of HIV-infected adults enrolled June 2005-July 2007. Eligible subjects were on ART with ≥2 nucleoside reverse transcriptase inhibitors (NRTIs), had HIV-1 RNA <10,000 copies/mL plasma, and no known diabetes or CVD. Clinical data were collected at each visit. Non-linear mixed-effect regression models were used to assess effects of BMI and lipid changes on hsCRP over time, adjusting for gender, age, race, smoking status, fasting state, protease inhibitor (PI) use, lipid-lowering therapy, CD4 count and HIV-1 RNA.

Results
94 subjects had data available from at least one visit, 65 from two visits, 41 from three visits, and 19 from four visits. Median age was 44 years, 27% were female, 43% of non-white race, 34% had clinical lipoatrophy, 17% on lipid-lowering therapy, and 54% on a PI. Median CD4, HIV-1 RNA, and hsCRP were 515 cells/mm3, <50 copies/mL, and 2.94 mg/dL, respectively. In multivariable repeated measures analysis adjusting for covariates, there were significant correlations between increased hsCRP and greater BMI (p=0.005), higher non-HDL (p=0.013) and triglycerides (p=0.017), and lower HDL (p=0.015).

Conclusions
In this group of HIV patients with low CVD risk and virologic suppression on ART, hsCRP was independently associated with BMI and serum lipid changes. These results suggest that hsCRP may be of value for assessing certain HIV-infected patients for metabolic complications and CVD risk on ART. Future studies should assess associations between hsCRP and clinical outcomes.
CEREBRAL TISSUE MONITORING DURING SHUNT ASPIRATION IN PEDIATRIC PATIENTS WITH HYDROCEPHALUS AND SHUNT MALFUNCTION

Timothy E Brenkert, MD, Cristina M Estrada, MD1, Thomas J Abramo, MD1 and Renee Miller, RN, BSN1

Background
Cerebral regional tissue (rSO2) values in pediatric hydrocephalus patients (pts) with and without malfunctioning shunts has been demonstrated to be reliable and consistent. During shunt malfunction, increased intracranial pressure results in changes to the brain's tissue perfusion, metabolism and oxygen extraction. Cerebral rSO2 values have been shown to be reflective of this occurrence. Ventricular shunt aspiration is for diagnostic purposes and reduces intraventricular and intracranial pressure. Improved cerebral perfusion and oxygen delivery should be reflective in cerebral rSO2 values.

Objective
This study aims to determine the reliability and consistency of cerebral rSO2 values during ventricular shunt aspiration.

Methods
A prospective observational study of pediatric hydrocephalus pts presenting to the PED with confirmed malfunctioning shunts requiring aspiration was performed. Pts had INVOS NIR probes placed on the right and left forehead, and were continuously monitored until shunt was aspirated and up to 2 hours post procedure or until they departed the PED.

Results
Seven patients had cerebral rSO2 monitoring during shunt aspiration. Four males, 5 pts with right sided shunts. Age: 2.5 SD ± 5.1 yrs. Five pts had proximal shunt malfunction, 2 had distal. Pre-shunt tap: Overall average forehead readings in %, left, range 60-85, mean 72.8 ± 4.4; right, range 56-83, mean 67.8 ±4.9. Left sided readings were significantly higher than the right (p < 0.0001) by paired t-test, with a mean difference of 8.6, 95%CI (8.28, 9.01). Intra-class correlation coefficient (ICC) for left channel readings was 0.84; ICC for right sided readings was 0.66, indicating more consistency in left sided readings than the right. Post-shunt tap: Overall average forehead readings in %, left, range 57-87, mean 71.2±4.0; right, range 62-86, mean 70.0±3.8. Left sided readings were significantly lower than the right (p=0.006) by paired t-test, with a mean difference of -0.32, 95%CI (-0.55,-0.09). ICC was 0.89 for left sided readings and 0.85 for the right. ICC increased post-tap on the right indicating that within-subject variance was larger before shunt tap, and better consistency was seen after shunt tap.

Conclusions
Preliminary data demonstrate reliable and consistent cerebral rSO2 values during shunt aspiration in pediatric hydrocephalus pts with malfunctioning shunts. Further studies of cerebral rSO2 monitoring during shunt aspiration are in progress.
IDENTIFICATION OF FACTORS THAT INFLUENCE PARENT ATTITUDES TOWARD TYPE 1 DIABETES CLINICAL RESEARCH

Daniela Buscariollo, Mario A. Davidson, PhD, Russell Rothman, M.D., M.P.P., William E. Russell, M.D., Daniel J. Moore, M.D., Ph.D.

Objectives
To identify factors that influence parental willingness to enroll their children in Type 1 Diabetes clinical trials (T1DCTs).

Methods and Materials
Input from local diabetes experts was used to identify key domains that were expected to influence parent attitudes. Survey questions were then generated to probe these domains. The survey was refined through feedback from parent focus groups and a pilot test at a diabetes day camp. The final survey consisted of 48 questions including open-ended, yes/no, and Likert response formats. Surveys were then distributed at Diabetes Family Day (DFD) (n=21) and the Eskind Pediatric Diabetes Clinic 11/12/08-11/21/08 (n=67). All participants were parents of pediatric T1D patients. Response rate was based on total attendance at DFD and the number of T1D patients seen at Eskind during the defined period.

Results
Response rate was 57% and respondents were predominantly Caucasian (95%) females (79%). 75% of respondents reported awareness of T1DCTs at Vanderbilt. Nearly 50% described themselves as willing to enroll. Willingness to enroll was positively influenced by whether participants had received easy-to-understand information about T1DCTs from a healthcare provider (r=0.55, p<0.01). Self-reported income and concern about diabetes complications positively correlated with willingness (r=0.25 and 0.33, p<0.05). Only 20% recalled being asked to enroll a child in a T1DCT by a healthcare provider. Less than 30% of parents reported comfort with T1DCT protocols using IV medications, vaccines, or placebo. Parents reporting themselves as more willing to enroll in T1DCTs were more likely to accept these trials (r=0.26-0.49, p<0.01).

Conclusions
Parents report willingness to enroll their children in T1DCTs. However, only a minority accept methods in current trials. Information from healthcare providers can significantly influence parent willingness. Thus, efforts to increase awareness of T1DCTs and their methods may accelerate testing of new therapies for T1D.
LABORATORY PRACTICES FOR THE DETECTION OF SHIGA TOXIN-PRODUCING E. COLI

Lane Crawford, VMS II
Emphasis mentor: Charlene Dewey, M.D., M.Ed.

Objectives
Shiga toxin-producing E. coli (STEC) is an important cause of diarrheal illness, hemorrhagic colitis, and hemolytic-uremic syndrome. The most commonly isolated serotype of STEC in the United States is E. coli O157:H7, but current literature reports that non-O157 serotypes cause 20-50% of STEC infections in this country. Currently, most clinical laboratories screen for STEC by culture on sorbitol-MacConkey agar (SMAC), which does not detect non-O157 serotypes. Over the past two decades, a number of rapid immunological Shiga toxin assays that detect all STEC serotypes have been developed. In 2006, the CDC recommended that laboratories screen all stool specimens by Shiga toxin assay with simultaneous culture on SMAC. Adherence to this protocol offers significant clinical and public health benefits. The goals of this study were to describe current laboratory protocol for STEC detection in the state of Tennessee and to identify factors influencing choice of protocol.

Methods
Data was collected via scripted telephone or email interview with microbiology supervisors. Survey responses were entered into a coded electronic spreadsheet and analyzed for descriptive data only.

Results
Of 130 targeted labs, we received 117 responses (90% response rate). Of the labs that performed stool cultures in house, only 81% screened all specimens for STEC. Of the labs that tested some or all specimens for STEC, 70% used SMAC alone, 7% used Shiga toxin assay alone, and only 22% used both tests, as recommended by the CDC. We found that the most significant barriers to using Shiga toxin assay were lack of awareness about current literature and recommended protocol, high cost, and less convenient fit with laboratory workflow and staffing situation.

Conclusions
Our results suggest that laboratories in Tennessee have improved their adherence to recommended STEC detection protocol in recent years, but still fall far short of published guidelines. Improved clinical outcomes and public health response to emerging STEC infections will require greater education of health care providers regarding STEC detection and further implementation of CDC recommendations on a statewide level.
USE OF BIOMARKER RESPONSE TO CELECOXIB TO PREDICT RADIATION INDUCED LUNG AND ESOPHAGEAL TOXICITY: A STRATEGY TO INDIVIDUALIZE THORACIC RADIATION THERAPY

Ildiko Csiki, MD, PhD, Jason Morrow, MD, David P. Carbone, MD, PhD, David H. Johnson, MD, Bo Lu, MD, PhD

Objectives
Preclinical research shows that treatment with selective cyclooxygenase-2 (COX-2) inhibitors strongly enhances radioresponse of both rodent tumors and human tumor xenografts in nude mice. The hypothesis that inhibition of COX-2 activity enhances tumor response to radiation therapy without increasing the risk of treatment related toxicities has been recently examined in a phase II trial at Vanderbilt University using celecoxib in combination with chemo-radiotherapy for patients with non-small cell lung cancer (NSCLC). We found that the urinary prostaglandin E2 metabolite (PGE-M) is a promising biomarker for predicting response to COX-2 inhibition in NSCLC. A significant concern during lung radiation treatment is development of pulmonary and/or esophageal toxicity. Our goal was to correlate clinical response with toxicity development during therapy and to identify biomarkers that may be able to predict radiation-induced lung and esophageal toxicity.

Methods
We correlated the pulmonary and esophageal toxicity of NSCLC patients receiving celecoxib while undergoing concurrent chemo-radiation with their clinical response and urinary PGE-M levels as measured by mass spectrometry.

Results
We find that the incidence of esophageal and/or pulmonary toxicity correlated with clinical response, such that patients with stable (SD) or progressive disease (SD) after therapy were more likely to experience Common Toxicity Criteria (CTC) grade 2 or higher esophageal and/or pulmonary toxicity compared to patients with a partial response (PR). Pulmonary toxicity was noted in 55.5% of patients with PD/SD whereas none of the patients with PR experienced pulmonary toxicity. Esophageal toxicity was seen in 44.4% of patients with PD/SD and 16.6% of patients with PR. Average pre-treatment PGE-M levels in patients with pulmonary and esophageal toxicity were 52.8ng/ml and 52.7 ng/ml, compared to patients who did not experience these toxicities (12.5ng/ml).

Conclusions
We find that a short course of celecoxib prior to concurrent chemo-radiation for NSCLC may aid in identifying patients that are more likely to experience significant and potentially therapy-limiting toxicity. Furthermore, identification of biomarkers or models that can accurately predict radiation-induced lung or esophageal damage at an early stage, before completion of chemo-radiation, would allow physicians to tailor therapy to alter the toxicity profile.
VARIABILITY IN RESPONSE TO BETA-BLOCKADE: THE EFFECT OF GRK5 GENETIC VARIATION

A. J. Cunningham,1 C. Li,2 G. G. Sofowora,1 E. A. Friedman,1 M. Muszkat,1 U. Kohli,1 U. B. Menon,1 A. J. Wood,1 C. M. Stein,1 D. Kurnik1;
1Clinical Pharmacology, Vanderbilt University, Nashville, TN,
2Center for Human Genetics Research, Vanderbilt University, Nashville, TN

Objectives
A common functionally significant polymorphism in G protein-coupled receptor kinase 5 (GRK5-Leu41) encodes a gain-of-function enzyme that enhances desensitization of the b1-adrenergic receptor (ADRB1). GRK5-Leu41 was associated with improved outcomes in heart failure and was postulated to confer endogenous “genetic b-blockade” and to explain attenuated responses to b-blockade observed in African Americans (Nature Medicine, 2008, Liggett SB). The effects of this GRK5 variant on sensitivity to a b-blocker have not been studied in humans.

Methods
We measured heart rate at rest and during graded incremental exercise (25, 50, 75W for 2 min each) in 154 healthy subjects (85 Caucasian, 69 African American) before and after oral administration of 25mg atenolol. Variants of GRK5 (Gln41Leu) and ADRB1 (Ser49Gly, Arg389Gly) were determined and plasma atenolol concentrations measured. The effect of genotype and other covariates on sensitivity to atenolol, measured as the reduction in exercise-induced tachycardia, were determined using multiple regression analyses.

Results
As we reported previously, African American ethnicity (P=0.006) and ADRB1 Gly389 (P=0.003) were independently associated with a smaller reduction in exercise-induced tachycardia after atenolol. GRK5-Leu41 (32.6% of African Americans and 0% of Caucasians) had no effect on baseline heart rate before (P=0.61) and after adjustment for age, sex, ethnicity, atenolol concentrations, BMI and ADRB1 genotypes (P=0.81). Similarly, the decrease in heart rate after atenolol did not differ significantly according to GRK5 genotype at rest, at maximal exercise or exercise heart rate-AUC, before (all P>0.14) and after statistical adjustment for covariates (all P>0.17).

Conclusions
The GRK5-Leu41 allele does not affect response to b-blockade in vivo in healthy subjects, nor does it account for the differences in response observed among African-Americans and Caucasians.
OBJECTIVE AND SUBJECTIVE COMPARISON OF 3T AND 7T MRI OF THE BRAIN

Aditi Desai; Jeff Creasy, MD; Cari Buckingham, MD; Emma Bisson, MD; Brian Welch and Calum Avison, PhD

Objectives
Ultra high field (7T) MRI offers higher resolution images with enhanced signal-to-noise ratios (SNR), contrast-to-noise ratios (CNR), and image quality that may enhance detection of neuropathologies, yet not much literature exists comparing 7T MRI to clinical field strengths (3T). This study compares 7T and 3T MRIs of the brains of the same patients to objectively and subjectively assess the strengths and limitations of 7T MRI.

Methods
22 patients undergoing clinical 3T scans were consented for a 7T scan. Image volumes of 3 comparable sequences at each field strength were graded by two neuroradiologists for anatomic visualizations, gray/white matter differentiation, image uniformity, and artifact severity. 3 healthy volunteers were consented for duplicate scans at 3T and 7T to calculate SNR of caudate, putamen, and thalamus, and CNR of frontal, parietal, and occipital lobe gray/white matter at 3 comparable sequences at each field strength.

Results
2D fast field echo sequences demonstrated statistically significant increases of SNR of the putamen (212%, p<0.01) and thalamus (194%, p=0.02), and of CNR of occipital lobe gray/white matter (460%, p=0.01). T1-weighted 3D turbo field echo sequences showed statistically significant increases of SNR of the putamen (190%, p=0.02) and thalamus (186%, p=0.04), and of CNR of frontal lobe (202%, p=0.03) and parietal lobe gray/white matter (184%, p=0.01). Grading of 3T and 7T images is incomplete.

Conclusions
Preliminary objective analysis of 7T versus 3T MRI demonstrates improved SNR of putamen and thalamus, and improved CNR of various cortical gray/white matter areas at multiple sequences, suggesting improved image resolution and quality. Subjective analysis pending.
NATIONAL VARIABILITY IN THE RATES OF PROPHYLACTIC VENA CAVA FILTERS AMONG US TRAUMA CENTERS

Lesly A Dossett, MD/MPH; Raeanna C Adams, MD; and Bryan A Cotton, MD/MPH

Objectives
Prophylactic inferior vena cava filter (PICVF) placement has increased in trauma patients. Guidelines for PICVF vary from (1) not recommended to (2) recommended in patients with a contraindication to anticoagulation and a high risk injury. Our objective was to determine the national variability in the placement of PIVCF among trauma centers.

Methods
The National Trauma Databank (NTDB) was queried for rates of PIVCF placement per high risk patient. High risk patients had (1) a contraindication to anticoagulation, and (2) a high risk injury pattern. Centers not submitting ≥1 procedure code and ≥1 diagnosis code were excluded. We also excluded patients <16 years old, and those with either a deep venous thrombosis or pulmonary embolism.

Results
1,630,385 patients (22,808 PIVCF) from 680 centers were eligible. Rates of PIVCF placement ranged from 0-1142 per high risk patient (Figure). Region (Northeast highest, West lowest) and state level designation (not designated highest, level III lowest) were the only center factors which led to different rates of PIVCF placement.

Conclusions
Patient and center characteristics only partially explain variation in PIVCF rates. Physician opinion, local culture, or other factors—rather than society guidelines—contribute to the variability in PIVCF rates demonstrated in the NTDB.
REHABILITATION AND MILD TRAUMATIC BRAIN INJURY-IS OUT-REACH THE PROBLEM?

*John J. Eicken, BS, Susan Lattimore, Mario Davidson, PhD, Oscar Guillamondegui, MD*

**Objectives**
To determine the barriers associated with access to post-injury cognitive rehabilitation in mild traumatic brain injury (TBI).

**Methods**
A retrospective cohort pilot study of 234 mild TBI patients who sustained their injury between July 2005 and 2007 and were treated at a Level I trauma center were evaluated by phone survey utilizing the Glasgow Outcome Score (GOS) at least 6 months post-discharge. The cohort was blunt trauma patients with a GCS 13-15, history of concussion/amnesia, negative head CT findings, a working phone number, living in a major metropolitan area and contiguous counties ensuring access to adequate cognitive rehabilitation services. Data was culled from a dedicated trauma database. Patients without post-injury cognitive rehabilitation were asked follow-up questions concerning access. All patients received TBI literature prior to discharge and were contacted by the Tennessee TBI foundation post-discharge, per state regulation. Statistical analysis by chi-square where indicated.

**Results**
Of 379 eligible patients, 234 completed the phone survey. 211 patients did not receive rehabilitation with 28% believing post-injury rehabilitation was necessary. 24% did not recover to the quality of life prior to injury (GOS<5). Nearly two-thirds (61%) were unaware of post-injury rehabilitation services. An association between GOS and insurance status (p-value= .01) was identified.

**Conclusions**
Within a major metropolitan region, nearly a quarter of individuals suffering mild TBI did not recover to baseline. 28% of patients subjectively felt they needed rehabilitation. Even with provided literature and follow-up contact, almost two-thirds of patients with mild TBI were unaware that cognitive rehabilitation was available. There is evidence to suggest patient recovery from mild TBI is associated with insurance status. Further research is required to identify outreach and access to care improvement in this population.
A BRIEF VIOLENCE PREVENTION INTERVENTION AFFECTS PARENT’S ATTITUDES TOWARD SPANKING

Seth J. Scholer MD, Emma C. Hamilton, Melissa C. Johnson, Theresa Scott

Background
Physical punishment is a risk factor for childhood aggression.

Objective
To determine if a brief intervention can affect parents’ attitudes toward physical punishment.

Methods
Parents were recruited from a preschool, a primary care clinic and a nurse home visitation program. The intervention group viewed between 8 and 16 strategies for responding to aggression in the Play Nicely program; viewing time ranged from 8 to 20 minutes. The control group viewed a 5 minute section of the program focused on decreasing exposure to violence. Researchers, blinded to the treatment allocation, collected baseline data and completed a phone call follow up on 67% (67/100) 1-8 months after enrollment. A key measure was the Attitudes Toward Spanking (ATS) scale which is correlated with use of physical punishment; parents who use more spanking have higher scores.

Results
All (100%) parents agreed that they were pleased that the program was provided to view. Most (88%) stated that they planned to change how often they use certain options to respond to hurtful behavior with their children. Comparing the control group with the intervention group at follow-up, there was no difference in the ATS score. Within group analysis demonstrated a 2 point decrease in the ATS score for the intervention group (p=.045). Ten parents in the intervention group stated that they planned to do less spanking immediately after the viewing; this subset of the intervention group had a 5 point decrease in the ATS score (p=0.017) at follow up. Within group analysis did not demonstrate a shift in the ATS score for the control group (Table 3).

Conclusions
A brief intervention lasting less than 20 minutes shifts parental attitudes about corporal punishment. Parents who verbalized a planned reduction in spanking had a larger shift in their attitudes. The results have implications for violence prevention.
USING A LARGE ELECTRONIC MEDICAL RECORD TO VALIDATE 4Q25 VARIANTS CONFERRING RISK FOR ATRIAL FIBRILLATION

Joshua Denny, Marylyn Ritchie, Dana Crawford, Andrea Havens, Justin Weiner, Hiroshi Watanabe, Dawood Darbar, Prince Kannankeril, Jill Pulley, Melissa Basford, Jonathan Haines, Dan Masys, Dan Roden

Background
Genome-wide association studies, largely in research populations, have identified susceptibility single-nucleotide polymorphisms (SNPs) for a broad range of human diseases, including variants at 4q25 associated with atrial fibrillation (AF). However, no studies have evaluated the applicability of these data to practice-based settings.

Methods
This study was conducted in the Vanderbilt DNA Databank, a repository that accrues 500-900 new samples/week from routine outpatient blood draws, and included 37,335 samples as of June 2, 2008. The Databank is linked to a de-identified derivative of the Electronic Medial Record (EMR), which includes data for the last 15 years on 1.4 million subjects. We used natural language processing techniques and billing code queries to extract AF cases and controls (no AF) from the first 10,000 subjects entering the Databank. Cases had AF recorded in the cardiologist report of an electrocardiogram (ECG). Controls had at least one ECG and no mention of AF, other abnormal atrial rhythms, or atrioventricular nodal ablation in any portion of the EMR, including text documents, billing codes, and ECGs. Subjects with heart transplants were excluded. Subjects were genotyped at rs2200733 and rs10033464, both located at 4q25, previously associated with AF with Odds Ratios (OR) of 1.75 and 1.39, respectively.

Results
We identified 168 cases with AF and 1695 controls (no AF). The electronic algorithms had an accuracy of 98% for identifying cases and 100% for controls over a random sample of 100 subjects each. In this study, we replicated the previous association of rs2200733 [OR = 1.44 (1.01-2.03, p=0.04)] with AF. We did not replicate the effect for rs10033464 [OR = 1.14 (0.78-1.67, p=0.52)]; however power calculations indicate that 993 cases were needed to replicate this effect. The minor allele frequency (MAF) for rs2200733 was 0.1419 for cases and 0.1032 for controls; the MAF for rs10033464 were 0.1019 for cases and 0.908 for controls.

Conclusion
This practice-based study replicated an association identified in research datasets between a 4q25 SNP and AF. These findings support the utility of Electronic Medical Records coupled to DNA collections as resources for genomic research.
PHOSPHODIESTERASE 5 INHIBITION IMPROVES BETA CELL FUNCTION IN THE METABOLIC SYNDROME

Kevin D. Hill, M.D., Aaron W. Eckhauser, M.D., Annis Marney, M.D., Nancy J. Brown, M.D.

Objectives
Nitric oxide and cGMP contribute to beneficial effects of ACE inhibition on glucose homeostasis in animal models. This study tested the hypothesis that administration of a phosphodiesterase 5 inhibitor alone or in combination with an ACE inhibitor would improve insulin sensitivity, beta cell function, and fibrinolysis in individuals with the metabolic syndrome.

Methods
Insulin sensitivity and beta cell function (frequently sampled IV glucose tolerance test) and fibrinolytic parameters were measured in 18 adults meeting National Cholesterol Education Panel criteria for the metabolic syndrome during carbohydrate-controlled diet after randomized, double-blind, 3-week treatment with placebo, ramipril (10mg/d), tadalafil (10mg/od), and ramipril + tadalafil.

Results
Ramipril decreased systolic blood pressure (118.9±11.9mmHg versus 125.9±16.6mmHg during placebo, p=0.01) and diastolic blood pressure (75.0±8.0mmHg versus 82.0±12.4mmHg during placebo, p=0.001). Tadalafil did not affect blood pressure overall, but lowered diastolic blood pressure in whites (p=0.05 for effect of tadalafil, p=0.02 for ramipril x tadalafil interaction). Ramipril did not affect insulin sensitivity or beta cell function. Tadalafil significantly improved beta cell function (p=0.01). In subgroup analysis, this effect was observed in women (331.9±209.3mu/mM during tadalafil versus 154.4±48.0mu/mM during placebo, p=0.01) but not in men, and in individuals with abnormal baseline fasting glucose (p=0.06) but not in those with normal baseline fasting glucose. There was no effect of ramipril, tadalafil or the combination on markers of fibrinolysis.

Conclusions
Phosphodiesterase 5 inhibition represents a novel strategy for improving beta cell function in the metabolic syndrome and may be particularly beneficial in women.
ASSESSMENT OF PULMONARY HYPERTENSION IN THE PEDIATRIC CATHETERIZATION LABORATORY: CURRENT INSIGHTS FROM THE MAGIC REGISTRY

Kevin D. Hill MD, D. Scott Lim MD, Allen D. Everett MD, D. Dunbar Ivy MD, J. Donald Moore MD

Objectives
Our objective was to assess current procedural practices in the cardiac catheterization laboratory when assessing pulmonary hypertension (PH) in the pediatric patient.

Methods
We reviewed the PH registry data from the 17 pediatric interventional programs participating in the Mid-Atlantic Group of Interventional Cardiology (MAGIC) collaboration. Data was assembled by the MAGIC data use committee.

Results
Between 01/2003 and 10/2008, 7/17 institutions submitted data from 178 pediatric patients (ages 1mo-18yrs, mean 46.5±51.9mo) undergoing an initial cardiac cath at that center for suspected PH. In 74% of cases general anesthesia (GA) was utilized. Arterial access was obtained in 93% and left heart cath was performed in 70%. Vasodilator testing was utilized in 94%. Nitric oxide and oxygen were the primary vasodilators used in 85% and 81% respectively. 35% were deemed responsive. Diagnosis and cath demographics are listed below.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
<th>Age (yr)</th>
<th>Mean PAP (mmHg)</th>
<th>Mean PAP (% systemic)</th>
<th>PVR (Wood units/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD shunt related</td>
<td>60 (34)</td>
<td>3.0±4.8</td>
<td>38.3±17.1</td>
<td>67.6±26.8</td>
<td>6.6±5.3</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>34 (19)</td>
<td>6.8±5.7</td>
<td>52.9±20.7</td>
<td>82.2±27.7</td>
<td>14.4±10.4</td>
</tr>
<tr>
<td>BPD related</td>
<td>23 (13)</td>
<td>1.2±1.6</td>
<td>35.3±13.2</td>
<td>60.3±17.1</td>
<td>7.5±4.7</td>
</tr>
<tr>
<td>Persistent PH of newborn</td>
<td>11 (6 )</td>
<td>0.6±0.6</td>
<td>31.3±17.0</td>
<td>58.8±27.9</td>
<td>4.1±2.8</td>
</tr>
<tr>
<td>CDH related</td>
<td>8 (4 )</td>
<td>2.5±1.9</td>
<td>31.5±8.9</td>
<td>52.1±22.5</td>
<td>5.8±1.0</td>
</tr>
<tr>
<td>Assoc. with left heart Dz.</td>
<td>9 (5 )</td>
<td>4.6±5.0</td>
<td>40.1±15.5</td>
<td>67.1±21.1</td>
<td>7.0±4.5</td>
</tr>
<tr>
<td>Other</td>
<td>44 (18)</td>
<td>4.1±11.3</td>
<td>33.0±14.2</td>
<td>52.5±19.8</td>
<td>6.1±4.3</td>
</tr>
</tbody>
</table>

64% of patients had baseline mean PA pressures below 40mmHg. However, of that group, 71% had RV pressures >50% systemic pressure. After controlling for age and diagnosis, use of GA significantly lowered baseline systemic pressures (p<0.01) but did not significantly affect cardiac index, mean PA pressure, pulmonary vascular resistance or systemic vascular resistance. There was poor correlation between echo estimates of RV systolic pressure and pressures obtained at catheterization (R²=0.29). Adverse events were rare (n=7). No procedural deaths were reported.

Conclusions
Pediatric PH currently includes a heterogenous disease spectrum. As such, diagnostic approaches and current definitions of reactivity may prove problematic, particularly in younger patients whose baseline PA pressures are only mildly increased yet elevated relative to systemic pressure. General anesthesia did appear to affect baseline systemic pressures but not other hemodynamic parameters. Complications in this high risk group of patients were rare.
THE EFFECT OF SHORT INTERPREGNANCY INTERVAL ON PRETERM BIRTH RATES IN TN

Ernestine Jideama, B.A, VMS III, William Walsh MD

Introduction
Tennessee boasts some of the worst statistics for birth outcomes in the nation. In 2008, the state ranked 48th in the number of premature births. Preterm birth (PTB) is the leading cause of infant mortality and is responsible for 1/3rd of all infant deaths. An important risk factor for preterm birth is interpregnancy interval (IPI). It is known that short IPI (IPI <12 months) is associated with higher rates of preterm birth in the subsequent pregnancy. However, how this risk factor affects Tennessee’s high rates of PTB has not been elucidated.

Objectives
To determine the role short IPI has on Tennessee’s rate of PTB by evaluating whether mothers with short IPI have higher rates of PTB in TN.

Methods
The study was a retrospective, historical cohort study that analyzed Birth and Hospital Discharge datasets provided by the TN Department of Health. This previously collected data of all mothers who gave birth between 1998 and 2002 in TN and have had a past term or preterm birth in the past was examined (N=223,450).

Results
The proportion of women who had an infant death and an IPI between 6 and 12 months was higher (20%) than those with an IPI between 12 and 18 months (16%),(p-value < .001). The odds of a mother with short IPI of 3-6 months having an infant death is 1.75 times more likely than mothers with longer IPI’s greater than 18 months.

Conclusions
Data from this large dataset suggest that short IPI is a significant risk factor for infant mortality in the state of Tennessee. Present public policy requires post-partum insurance coverage for women for only 8 weeks. If this benefit were extended to provide post-partum coverage including birth control for a year, there could be a significant improvement in infant mortality in TN.
DEEP BRAIN STIMULATION: ITS EFFECT ON RATE OF INCREASE OF ANTIPARKINSONIAN MEDICATION

Kahn EN, Gill CE, Davis TL, Putman MS, Holt HK, Cook JA, Song Y, Bowman AB, Charles PD

Objectives
Primate data suggest that subthalamic nucleus deep brain stimulation (STN-DBS) may slow disease progression in Parkinson’s Disease (PD). The effect has not been studied in humans due to ethical implications of withholding treatment from advanced PD patients. Change in anti-PD medication reflects disease progression in the absence of direct measurement.

The purpose of this study was to compare rates of increase of anti-PD medication between patients who receive STN-DBS versus medication-only patients.

Methods
Clinic records were queried for patients with PD who had received bilateral STN-DBS (DBS arm). Ten subjects were randomly selected and PD patients who had not received DBS (MED arm) were matched by age at first anti-PD therapy. Levodopa Equivalent Daily Dose (LEDD) at each clinic visit was calculated using previously published equivalency formulas. Rate of increase was compared between groups using a mixed-effects model with random intercept and follow-up by treatment interaction.

Results
The rate of increase in anti-PD medication overall was similar in MED and DBS subjects (p=0.198).

Conclusions
We found similar dose increase rates in medication-only and DBS patients, which does not support a potential neuroprotective effect of STN-DBS. The non-significant result may be due to small sample size and large between-subjects variability.
REDUCTION IN MONOCYTE MEMBRANE CD36 EXPRESSION AND ELEVATION OF MEMBRANE INSULIN RECEPTOR EXPRESSION IS NOT RELATED TO WEIGHT LOSS FOLLOWING BARIATRIC SURGERY

Nader R. Kasim, Robyn A. Tamboli, Pamela A. Marks, Brandon Williams, Robert O. Carpenter, Willie Melvin, William O. Richards, and Naji N. Abumrad

Objectives
Obesity is associated with significant cardiovascular co-morbidities; weight loss due bariatric surgery (BS) is associated with significant improvements of these co-morbidities. In this study we examined the effect of early weight loss induced by BS on the expression of CD36, a scavenger receptor involved in atherosclerotic plaque formation and considered a marker of insulin sensitivity, in two monocyte populations: classical (CD14⁺CD16⁻) and proinflammatory (CD14⁻CD16⁺). We also determined membrane expression of insulin receptors (IR) as a surrogate of insulin function in morbidly obese subjects.

Methods
Six bariatric patients were studied before and 10 days after BS. Blood samples were obtained for flow cytometry to quantitate CD36 and IR levels and identify monocyte subpopulations.

Results
BS resulted in a 2.4 kg weight loss (p = 0.1563); mean preoperative and postoperative body weight was 125.7 ± 4.8 and 123.3 ± 4.1 kg, respectively. CD36 decreased 20% and 27% in CD14⁺CD16⁻ and CD14⁻CD16⁺ monocytes, respectively. Furthermore, IR increased 43% and 17% in CD14⁺CD16⁻ and CD14⁻CD16⁺ monocytes, respectively. Preoperative and postoperative CD36 and IR expression in CD14⁺CD16⁺ monocytes was 3-5 times higher than CD14⁺CD16⁻ monocytes. There were no changes in the relative frequencies for the two monocyte subsets postoperatively. All data comparisons were shown to be statistically insignificant.

Conclusions
Decreased plasma membrane CD36 and elevated IR in human monocytes were observed as early 10 days following BS, occurring prior to significant weight loss. Future inclusion of additional subjects in this study will help determine the importance of these preliminary findings.
ADRENERGIC RECEPTOR GENETIC VARIATION AFFECTS HEART RATE RECOVERY AFTER EXERCISE

Utkarsh Kohli, M.D., André Diedrich, M.D., Ph.D., Prince J Kannankeril, M.D., Mordekhai Muszkat, M.D., Gbenga G. Sofowora, M.D., C. Michael Stein, M.D., Daniel Kurnik, M.D.

Objectives
Heart rate recovery after exercise is a predictor of future adverse cardiovascular outcomes and is partly mediated by sympathetic withdrawal. Alpha2 adrenergic (ADRA2) receptors mediate decreased sympathetic activity and beta adrenergic receptors (ADRB1 and ADRB2) mediate heart rate responses to sympathetic stimulation. We tested the hypothesis that common adrenergic receptor polymorphisms affect heart rate recovery after exercise.

Methods
126 (66 Caucasians, 56 African Americans; 70 females) subjects exercised at incremental loads (25, 50 75 W) each for two minutes. ECG recordings were obtained during and after exercise and an exponential curve was fitted to the post-exercise RR intervals for each subject to calculate the recovery constant (k). We also measured the decrease in heart rate one minute after stopping exercise (\(\Delta HR_{1\text{min}}\)). Multiple linear regression models adjusted for age, sex, race, and a fitness index derived from exercise history were used to define the effect of common adrenergic receptor (9 ADRA2A, 1 ADRA2B, 5 ADRA2C, 2 ADRB1 and 3 ADRB2) genetic variants on \(\Delta HR_{1\text{min}}\) and k. An additive effect was assumed for analysis.

Results
Heart rate recovery after exercise as determined by the k values was faster in ADRA2B 301_303 deletion carriers (n=64) (\(\beta\) coeff.=-.003; P=0.01). The variant alleles of ADRA2A rs11195418 (mean adjusted difference [\(\Delta\)] = -7.1, 95% CI -13.9 to -0.25 beats/min; P=0.042), rs1800545 (\(\Delta\) = -2.9, 95% CI -5.7 to -0.2 beats/min; P=0.036) and rs3750625 (\(\Delta\) = -3.5, 95% CI -7.0 to -0.09 beats/min; P=0.045) were associated with a significantly slower decrease in heart rate after 1st minute of recovery compared to the wild type allele.

Conclusions
Genetic variability in adrenergic receptors contributes to interindividual variability in heart rate recovery after exercise, and may underlie part of the genetic predisposition to adverse cardiovascular outcomes.
ATRIAL FIBRILLATION AND INFLAMMATION: MODULATION BY ACE INHIBITORS AND STATINS

Jie Li, MD, Joseph Francis Solus, PhD, Shannon Carter, RN, Gayle Ann Kucera, RN, Young Hee Rho, MD, PhD, Jeff Rottman, MD, C. Mike Stein MD, Dawood Darbar MD, PhD.

Background
Increasing evidence links inflammation to cardiovascular disorders such as coronary artery disease and hypertension. Similarly, there is emerging data that inflammation is associated with atrial fibrillation (AF). We investigated the association of AF with systemic inflammation and determined if the inflammatory response is modulated by statins and ACEIs, drugs postulated to have anti-inflammatory effects.

Methods
We studied 219 consecutive patients enrolled in the Vanderbilt AF Registry and 60 age-matched controls and obtained a detailed medical and medication history. AF was categorized as paroxysmal, persistent and permanent. Serum levels of interleukin (IL)-1, IL-6, IL-8, IL-10, TNF, MCP-1, VEGF and NTpBNP were measured.

Results
Median concentrations of IL-8 (11.3 vs 4.4 pg/ml), TNF-α (5.5 vs 1.9 pg/ml), MCP-1 (230.4 vs 143.2 pg/ml), VEGF (77.3 vs 33.2 mg/dl) and NTpBNP (244.0 vs 25.3 pg/ml) were significantly higher in AF patients than controls (all P values < 0.001). NTpBNP concentrations were higher in patients with non-lone AF (n=155) than those with lone AF (n=55) (349.1 vs 84.1 pg/ml, P<0.001) with no significant difference in cytokine concentrations. IL-10 (4.2 vs 1.9 pg/ml P<0.05) and NTpBNP (588 vs 104.3 pg/ml, P<0.001) were the only two biomarkers that were elevated in patients with permanent AF compared to paroxysmal AF. In sub-group analysis, patients receiving statins and ACEIs had no differences in cytokine concentrations but NTpBNP concentrations (statin vs no statin: 354.4 vs 148.7 pg/ml P=0.074, ACEI vs no ACEI: 404.4 vs 142.5 pg/ml, P<0.05) were higher.

Discussion
These results provide evidence that inflammation may play an important role in the pathogenesis of AF. The degree of inflammation is similar whether patients are receiving statins and ACEIs or not. The etiology of elevated NTpBNP concentrations in AF patients receiving ACEIs and statins is unknown but likely reflects cardiac co-morbidities.
THE USE OF TWO-WEEK MORBIDITY CALENDARS TO ASSESS CLINICALLY RELEVANT ILLNESSES IN WOMEN IN RURAL WESTERN GUATEMALA

Robert B. Lindell, B.S., B.A.

Background
In 2002, Primeros Pasos opened as a clinical and educational resource for children in the Palajunoj Valley in western Guatemala. In 2006, the clinic began accepting adult patients and has seen tremendous growth in adult walk-in consultations. No other clinics provide health services to this population.

Objectives
To assess clinically relevant illnesses in women in the Palajunoj Valley through the use of two-week morbidity calendars.

Methods
Healthy 18-35 year old women without current medical symptoms were eligible for inclusion in the study. Participants were questioned regarding their experience of 20 common symptoms during the previous 14 days. For each positive symptom, the date of onset, duration, severity, source of treatment, and barriers to care were recorded. Constellations of concomitant symptoms were defined as illnesses, and illnesses treated in a clinic or self-reported as severe were defined as clinically relevant illnesses (CRIs).

Results
Of the 84 women surveyed, 32% experienced a CRI in the previous 14 days. The most common symptoms were sore throat, stomach pain, and cough. Compared to patients with non-serious symptoms, patients with a CRI were more likely to seek care in a clinic or seek advice from acquaintances. Patients with fever or GI symptoms were significantly more likely to seek clinical care than patients with respiratory symptoms. Despite familiarity with Primeros Pasos, 28% of patients with CRIs received no care from any source. Barriers to care were reported by 33% of patients and included cost, transportation, and child care.

Conclusions
The prevalence of illness in this community remains high despite access to clinical services. Understanding the barriers to care and the underlying prevalence of CRIs in the community will allow medical providers to better care for the health of this underserved population.
CEREBRAL TISSUE MONITORING IN PEDIATRIC PATIENTS WITH HYDROCEPHALUS AND SHUNT MALFUNCTION

Matthew R Locklair, MD, Cristina M Estrada, MD, Thomas J Abramo, MD and Renee Miller, RN, BSN

Objective
This study aims to determine the consistency and reliability of cerebral rSO\(_2\) in pediatric hydrocephalus patients with indwelling ventricular fluid shunts that present to the emergency department with shunt malfunction using near-infrared spectroscopy (NIR). NIR is a noninvasive technique for evaluation of oxygen availability and consumption. Prior pediatric studies have demonstrated NIR's utility and reliability in measuring cerebral tissue oxyhemoglobin saturation (rSO\(_2\)) and detecting cerebral perfusion changes in asymptomatic patients with shunted hydrocephalus.

Design/Methods
A prospective observational study of pediatric hydrocephalus patients presenting with signs and symptoms of malfunctioning shunts was performed. Patients had NIR probes placed on the forehead with continuous monitoring until the patient left the ED. Patients were included if they had NIR monitoring with an abnormal shunt series ± Head CT, or shunt aspiration indicating malfunction. Cerebral rSO\(_2\) values were analyzed for consistency within and between patients.

Results
Thirty-six patients (pts) were enrolled (age 2 mo-17 yrs, mean 3.6yrs), 19 males. Twenty-seven pts had right sided shunts, 1 had bilateral shunts. Overall average readings, in %, left, range 42-95, mean 73.9 ± 10.6; right, range 32-95, mean 70.7 ± 11.2. Within-subject readings, in %, left, range 54-94, mean 70.8 ± 3.0; right, range 56-94, mean 70.8 ± 3.9. Left channel readings were significantly higher than the right (p < 0.0001) by paired t-test, with a mean difference of 2.3, 95% CI (2.19, 2.44). Intra-class correlation coefficient (ICC), the ratio of between subject variation to total variation, for left channel readings was 0.86; ICC for right channel readings was 0.79, both indicating good consistency of readings.

Conclusions
Reliable, consistent within-subject cerebral rSO\(_2\) tissue monitoring in pediatric hydrocephalus patients with malfunctioning shunts were demonstrated by NIR. Further studies are underway in hydrocephalus patients with shunts to compare their cerebral rSO\(_2\) values at functioning and malfunctioning shunt periods.
ADIPOCYTOKINES IN SYSTEMIC LUPUS ERYTHEMATOSUS: RELATIONSHIP TO INFLAMMATION, INSULIN RESISTANCE AND CORONARY ATHROSCLEROSIS

Cecilia P. Chung, M.D., M.P.H., Ashley G. Long, B.S., Joseph F. Solus, Ph.D., Young Hee Rho, M.D.; Annette Oeser, B.S; Paolo Raggi, M.D.; C. Michael Stein, M.D.

Objective
Adipocytokines secreted by adipose tissue affect insulin sensitivity, atherosclerosis and inflammation in the general population. Patients with systemic lupus erythematosus (SLE) have accelerated atherosclerosis and an increased prevalence of insulin resistance. We tested the hypothesis that concentrations of adipocytokines are altered in SLE and associated with coronary atherosclerosis, insulin resistance and inflammation.

Methods
Concentrations of resistin, leptin, adiponectin, and visfatin were measured in 109 patients with SLE and in 78 control subjects. Coronary calcification was measured by electron beam computed tomography and insulin resistance was defined by the homeostasis (HOMA) index.

Results
Concentrations of adiponectin (28.7+/-17.9 vs. 22.0+/-15.3 µg/mL, p=0.003), leptin (41.1+/-49.9 vs. 19.8+/-24.6 ng/mL, p<0.001) and visfatin (7.5+/-10.5 vs. 4.5+/-2.8 ng/mL, p<0.001) were higher in patients with SLE than controls. These differences remained significant after adjustment for age, race, sex and BMI, (All P values < 0.02). There were no significant differences in concentrations of resistin (10.7+/-7.6 vs. 9.1+/-5.1 ng/mL, p=0.41) in patients and controls. In patients with SLE, leptin (positively) and adiponectin (negatively) were associated with BMI (rho=0.80, p<0.001; rho=-0.40, p<0.001, respectively), insulin resistance (rho=0.46, p<0.001; rho=-0.38, p<0.001), and CRP (rho=0.30, p=0.002, rho=-0.22, p=0.02). None of the adipocytokines were associated with the presence or severity of coronary atherosclerosis in patients with SLE.

Conclusions
Patients with SLE have increased concentrations of adiponectin, leptin and visfatin. Lower concentrations of adiponectin and higher concentrations of leptin are associated with insulin resistance, BMI and CRP in patients with SLE. Adipocytokines are not associated with the presence or severity of coronary atherosclerosis in patients with SLE.
BNP INCREASES AS BMI DECREASES FOLLOWING ROUX-EN-Y GASTRIC BYPASS SURGERY

Annis Marney, Nancy Brown, Naji Abumrad

Objectives
Brain natriuretic peptide (BNP) predicts volume overload in patients with heart failure and predicts cardiovascular morbidity and mortality in the general population. Obesity is associated with inappropriately low BNP concentrations despite increased plasma volume and increased cardiovascular risk. BNP concentrations are partially nutritionally regulated and play a role in lipolysis. Short-term caloric restriction (≤6 months) has been shown to increase, decrease, or have no effect on BNP concentrations in obese subjects in various studies, but the long-term effects of bariatric surgery and caloric restriction on BNP are unknown.

Methods
To test the hypothesis that subjects undergoing sustained weight loss following bariatric surgery would experience an increase in BNP, we measured BNP in subjects at baseline and at multiple time points following Roux-en-Y gastric bypass surgery (RYGB). We obtained plasma samples from 38 obese subjects (36 female, 2 male, age 44±1 years, average baseline body mass index (BMI) 47.2±1.2 kg/m²) enrolled in a clinical trial comparing the effects of RYGB with or without omentectomy. We measured BNP at baseline, and at 4, 25, 52, and 104 weeks after surgery.

Results
BMI decreased at each time point after surgery (P<0.001 for comparison from baseline using Wilcoxon signed-rank test). BNP concentrations rose at time points 52 and 104 weeks after surgery (P<0.001 and P=0.008, respectively, using Wilcoxon signed-rank test). By linear mixed effects model analysis, BMI inversely correlated with the increase in BNP (P=0.005), whereas age, systolic blood pressure, hepatic function as measured by serum aminotransferases, hematocrit, and omentectomy versus no omentectomy were not associated with the increase in BNP (all P values >0.05).

Conclusions
These data suggest that substantial, sustained weight loss contributes to increasing BNP. The physiological consequences of this increase in BNP remain to be determined.
OSTEOPOROSIS RISK-ESTIMATION TOOLS: DEVELOPED BASED ON THE GROUP, APPLICABLE FOR INDIVIDUALS?

Laura Meints, Katherine Hartmann

Background
Risk-estimation models are frequently developed based on group data and then generalized to the individual level.

Objectives
Examine the applicability of individual risk-assessment models of osteoporosis for individual risk.

Methods
We took a mixed approach to this study question: 1) We searched PubMed/MEDLINE and Google for risk-estimation models of osteoporosis. Each risk-estimation model was searched for model components, component weights, scientific sources cited, and quality of data behind each model. 2) We developed six, hypothetical case examples of persons to assess risk of osteoporosis using the risk models identified. Each of the six, hypothetical case examples also had its characteristics varied in a permuted manner to verify component weights in each model. Finally, risk estimations were then analyzed for statistical and qualitative variation.

Results
Twelve risk-estimation tools for osteoporosis were identified in the literature. Substantial variation existed among these tools: 75% of tools cited at least one reference, 42% cited all references, 0% used BMI and only 50% used weight in the calculation of risk, 33% included gender in its calculation, 33% included ethnicity/race, and 42% included family history of fracture. Calculations of risk for the six, hypothetical case examples revealed wide variation in risk prediction for fracture due to osteoporosis and greater variation among cases with fewer evidence-based risk factors for osteoporosis-related fractures. For example:

<table>
<thead>
<tr>
<th>10 Year Fracture Risk</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 53, BMI 24, no personal history, no comorbidity</td>
<td>The majority of risk-prediction models for osteoporosis-related fracture are not designed for literal estimation of individual risk of fracture. Instead, they contain statistical validation and calibration at a population level without evaluation of discriminant diagnostic accuracy – thus, providing estimates for a population group yet not necessarily the individual woman. This limitation is little acknowledged within the related osteoporosis publications cited in risk-prediction models. Our findings suggest ethical issues concerning accuracy and promotion of information to the public that should be further investigated. In any case, risk-prediction tools designed for populations remain to an important degree embedded in clinical practice for use among individuals.</td>
</tr>
<tr>
<td>White low</td>
<td>6.5</td>
</tr>
<tr>
<td>White higher</td>
<td>13.0</td>
</tr>
<tr>
<td>Black low</td>
<td>2.9</td>
</tr>
<tr>
<td>Black higher</td>
<td>6.0</td>
</tr>
<tr>
<td>Hispanic low</td>
<td>3.5</td>
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<tr>
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<td>7.4</td>
</tr>
<tr>
<td>Asian low</td>
<td>3.5</td>
</tr>
<tr>
<td>Asian higher</td>
<td>7.2</td>
</tr>
</tbody>
</table>

1 = race/ethnicity data limited to “white” and “non-white”
2 = no option for race, 5-year risk calculation
DELIRIUM IN PEDIATRIC CRITICAL CARE: VALIDATION OF THE PEDIATRIC CONFUSION ASSESSMENT METHOD FOR THE ICU (PCAM-ICU)


Objective
The aim of this study is to validate the Pediatric Confusion Assessment Method for the ICU (pCAM-ICU) for the bedside diagnosis of delirium in ventilated and non-ventilated critically ill patients ages 5-18 years. Delirium is a commonly encountered medical condition in adult ICUs, exceeding 50% in some studies. It is associated with many poor prognostic indications including increased length of hospital stay, cost of care, morbidity, and mortality. Delirium has been understudied in the pediatric ICU population. The incidence, associated risk factors, appropriate preventative measures, treatment strategy, and overall prognosis for pediatric delirium have yet to be characterized. Study in this area has been hindered by the lack of a validated instrument to diagnose and monitor pediatric delirium by non-psychiatric trained clinicians.

Methods
The pCAM-ICU was administered by two ICU providers to 93 consecutively admitted patients to the Vanderbilt PCCU who met study inclusion criteria. Daily ratings were compared against psychiatric reference raters who used diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV, Text Revision.

Results
122 sets of observations (among 93 patients) with pCAM evaluations and psychiatry rating as a reference were collected to diagnose delirium. Only 16 patients were diagnosed with delirium by DSM-IV criteria. The sensitivity of the pCAM-ICU was found to be 81% though with 95% CI (0.48, 0.95). The specificity of the pCAM-ICU was found to 98% with 95% CI (0.94, 1.00). Only 15 ventilated observations were completed within the 122 total observations. From this initial evaluation, 50 additional non-verbal observations, will be required to strengthen the subgroup statistical analysis and prove the pCAM-ICU diagnoses delirium equally well in verbal versus non-verbal patients.

Conclusions
Preliminary data from the validation study of the pCAM-ICU support that this instrument has excellent sensitivity and specificity for screening and diagnosing delirium.
EXOSTOSES OF THE EXTERNAL AUDITORY CANAL IN WHITE WATER KAYAKERS

Ryan Moore, BS; Theodore Schuman, MD; Theresa Scott, MS; Scott Mann, BS; Robert LaBadie, MD, PhD

Background
Exostoses of the external auditory canal are benign tumors of the temporal bone associated with frequent cold water exposure. Obstruction may lead to conductive hearing loss and recurrent otitis externa, requiring surgery when symptoms become intolerable. While most commonly characterized in populations exposed to cold ocean surf, those exposed to white water rivers experience a similar environmental insult. Earplugs are often recommended as protection but have never been associated with decreased prevalence.

Objectives
To characterize the prevalence of exostoses in white water kayakers and identify significantly associated risk factors and protective habits.

Methods
Six-hundred eleven white water kayakers were included in the study (median age 30, range 7-68; from 9 kayaking festivals across the US in 2008). Percent occlusion (determined by video ostoscope) was graded as normal (<25%), minimal (<25% with discrete exostosis), mild (25-50%), moderate (50-75%), or severe (>75%). Subjects completed a survey of risk factors and protective habits. Kruskal Wallis and Chi-Squared tests were performed to determine significant associations with percent occlusion.

Results
The prevalence of exostoses in kayakers was 79% (482/611) – 30% (183/611) had ≥50% occlusion. Percent occlusion was associated with total years kayaked (p<0.001), frequency ≥ 1 day/week (p<0.001), male gender (p<0.001), age (p=0.005), and kayaking in the Pacific Northwest (p=0.018). Styles that involve repeated submersion were also associated (“freestyle” p=0.036; “squirt” p=0.016). In addition, those using earplugs showed greater frequency of exostoses (p=0.007). However, those using earplugs for a greater proportion of their kayaking career were less likely to have exostoses (p<0.001).

Funding was provided by an Alpha Omega Alpha Carolyn L. Kuckein fellowship and a Vanderbilt student research stipend. Various materials were donated by Deckers Outdoor Corporation.
SINGLE CENTER EXPERIENCE WITH ALLOMAP TESTING POST CARDIAC TRANSPLANT

Nawar, Mohamad A.; Adams, Sherrie; Dockins, Dottie M; Feurer, Irene; DiSalvo, Thomas G; Wigger, Mark A

Introduction
Allomap gene expression assay is used for non-invasive detection of acute cellular rejection (ACR) in heart transplant recipients. We report observational experience with AlloMap in clinically stable patients at annual assessment without biopsy.

Methods
Patients were identified based on assay availability, timing of annual assessment, and desire to participate between 8/2007 and 10/2008. Patients were ≥ 2 years from transplant, without rejection, and on stable immunosuppression. Annual protocol replaced endomyocardial biopsy (EMBx) with AlloMap and included stable patients who refused biopsy or lacked vascular access. AlloMap scores ≥ 35 were considered at risk for rejection and patients had repeat AlloMap, clinic visit, and echo at 4 weeks per protocol. EMBx obtained only if CHF symptoms persisted with high AlloMap score.

Results
110 clinically stable adult heart transplant recipients (88 male, 22 female) were tested at least once. 49 were tested ≥ 2 times for 177 total AlloMap tests. Median time post transplant was 134 months. AlloMap scores ranged from 14-39 and 49 patients had ≥ 1 score ≥ 35 (study group). These were compared to the remaining 61 patients with scores <35 (control group). The immunosuppressive regimens did not differ between patients with high and low AlloMap scores (non-significant Chi-square analysis). 28% of study group patients were associated with transplant vasculopathy versus 35% of control group patients (p=0.25). 40% of study group patients were associated with CRI (stage 3-5) versus 38% of control group patients (p=0.43). No high AlloMap scores were associated with ACR. Three patients with high scores and persistent CHF symptoms had negative biopsies.

Conclusion
In our observational experience, AlloMap test was a safe, non-invasive method of assessing ACR in cardiac transplant patients >5 years post transplant. AlloMap protocol resulted in enhanced patient satisfaction and reliable clinical outcomes to date. Our findings did not suggest that transplant vasculopathy and CRI are associated with high AlloMap scores in the absence of ACR. Study was limited by short-term follow-up and lack of longitudinal data. We recommend serial testing and adherence to a designed protocol using AlloMap as a non-invasive tool for management of cardiac transplant patients.
Background
Microalbuminuria, a biomarker of endothelial dysfunction, is associated with increased cardiovascular, renal, and cerebrovascular morbidity and mortality. The relationship between hypertension and microalbuminuria in relation to ethnicity is not completely understood.

Objectives
To compare the prevalence of microalbuminuria among JNC 7 blood pressure (BP) categories and to examine racial and ethnic differences in microalbuminuria among adults with prehypertension and hypertension.

Methods
16,567 US adults aged ≥20 years, were categorized according to JNC 7 BP definitions. Microalbuminuria was defined as spot urinary albumin creatinine ratio of 30 mg/g to 299 mg/g. Logistic regression estimated the odds of having microalbuminuria among BP categories compared with normal BP after adjusting for age, race, sex, education level, smoking status, body mass index, systolic BP, and diabetes status.

Results
Prevalence of microalbuminuria was 4.5% for normal BP, 6.3% for prehypertension, 12.4% for stage 1 hypertension, and 25.3% for stage 2 hypertension. Compared with participants with normal BP, the adjusted odds ratios and 95% confidence intervals for participants with microalbuminuria were 1.3 (1.1-1.7) for prehypertension, 2.0 (1.6-2.5) for stage 1 hypertension, and 4.9 (3.8-6.4) for stage 2 hypertension. Among participants with hypertension, non-Hispanic blacks (17.0%) and Mexican Americans (22.4%) were more likely to have microalbuminuria than non-Hispanic whites (13.4%).

Conclusions
Participants with hypertension and prehypertension had a higher likelihood of microalbuminuria than those with normal BP. The higher prevalence of microalbuminuria among non-Hispanic blacks and Mexican Americans suggests greater target organ damage in non-Hispanic blacks and Mexican Americans than in whites. Further research is necessary to determine if microalbuminuria can be used as a screening tool to identify adults at highest risk for target organ damage. These adults may need earlier pharmacologic intervention and more frequent clinical follow-up to prevent the progression of microalbuminuria.
Background
Little is known about geographic variations in hospitalizations for heart failure (HF), the most common principal discharge diagnosis for Medicare beneficiaries.

Objectives
This study investigates heart failure hospitalizations and examines geographical differences in hospitalization rates among Medicare beneficiaries in the Tennessee catchment area from 2000 to 2004.

Methods
Spatial analysis was used to examine trends in hospitalizations for HF as first-listed ICD-9-CM 428. All hospital claims for 2000 to 2004 were obtained from the Center for Medicaid and Medicare Services for Medicare beneficiaries aged ≥65 years in the Tennessee catchment area, which we defined as Alabama, Arkansas, Florida, Georgia, Kentucky, Mississippi, Missouri, North Carolina, Virginia, and Tennessee.

Results
The mean hospitalization rate for HF at the county-level was 25.12 per 1,000 Medicare-eligible beneficiaries, which compares to a mean county-level rate for the entire nation for the same period of 21.93 per 1,000. The county-level HF hospitalization rates for the catchment area ranged from 6.31 per 1,000 in Randolph County, Georgia to 76.67 per 1,000 in Clay County, Tennessee. The highest mean county-level HF hospitalization rate was in Mississippi (30.57 per 1,000), followed by Kentucky (29.18 per 1,000). The lowest mean county-level HF hospitalization rate was in North Carolina (21.68 per 1,000), closely followed by Virginia (21.79 per 1,000).

Conclusions
Major geographic differences exist in heart failure hospitalization rates among Medicare beneficiaries. Knowledge of these differences can inform heart failure program development and support; however the underlying determinants and mechanisms for these differences deserve further examination.

Hospitalization Rates for Heart Failure as First-listed Discharge Diagnosis among Medicare Beneficiaries, by County, Tennessee Catchment Area, 2000-2004
HYPOTHYROIDISM AFTER INTENSITY-MODULATED RADIATION THERAPY (IMRT) FOR HEAD AND NECK CANCER


Objectives
We conducted a retrospective review of 168 consecutively-treated locally advanced head and neck cancer (LAHNC) patients treated with intensity modulated radiotherapy (IMRT)/chemotherapy to determine the rate and potential risk factors for developing hypothyroidism post-treatment.

Methods
IMRT was delivered in 33 daily fractions to 6930 cGy to gross disease and 5610 cGy to clinically normal cervical nodes. Dose-volume histograms (DVHs) of IMRT plans were used to determine radiation dose to thyroid, and were compared to DVHs using conventional radiotherapy (3D-RT) in 10 of these same patients and to DVHs of 16 patients where the thyroid was intentionally avoided during IMRT. Weekly paclitaxel 30 mg/m² and carboplatin AUC-1 were given concurrently with IMRT.

Results
Fifty-six of 119 evaluable patients (47.1%) developed hypothyroidism after a median of 1.07 years post-IMRT (2.4 months to 3.9 years). Dose and volume of irradiated thyroid were associated with hypothyroidism development post-IMRT. Compared to 3D-RT, IMRT with no thyroid dose-constraints resulted in significantly higher minimum, maximum, median dose (p<0.0001) and percent thyroid volume receiving 10, 20, and 60 Gy (p<0.05). Compared to 3D-RT, IMRT with thyroid dose-constraints resulted in significantly lower median dose and percent thyroid volume receiving 30, 40, and 50 Gy (p<0.005), but significantly higher minimum and maximum dose (p<0.005).

Conclusions
If not protected, IMRT for LAHNC results in higher radiation to the thyroid than with conventional 3D-RT. Consequently, markedly higher post-treatment hypothyroidism and shorter latency is observed with IMRT. Techniques to reduce dose and volume of radiation to thyroid tissue with IMRT are achievable and recommended.
PRE-HOSPITAL HEALTH CARE PROVIDERS' ABILITY TO PREDICT CLINICALLY SIGNIFICANT TRAUMATIC INJURY: EMT AND PARAMEDIC ASSESSMENT VERSUS COMPUTED TOMOGRAPHY

Mario L. Ramirez, MD, MPP,† Jeremy Brywczynski, MD,* Cathy A. Jenkins, MS,‡ Clay Smith, MD,* Jared McKinney, MD,* Steven Meador, EMT-P,‡ Corey Slovis, MD, FACEP, FAAEM

Objectives
The 2006 Centers for Disease Control and Prevention (CDC) Guidelines recommend EMS provider judgment as a criteria when deciding whether to transfer trauma victims to a trauma center. However, no study to date has compared the in-field assessment of trauma patients by paramedics with clinically significant findings on full body CT scans. Our prospective study sought to compare paramedics' qualitative pre-scan assessment of significant injury to the imaging results.

Methods
Paramedics transporting any level one or two trauma patient who was at least 15 years of age anonymously completed a Likert scale survey assessing the probability of "clinically significant injury" based on different scene variables. Following CT scan, the actual findings were compared to the paramedics' assessments by a third party. Sensitivity, specificity, positive predictive value, and negative predictive values were computed across various mechanisms of injury. Logistic regression models were fit to test for associations between paramedic and CT findings across several variables.

Results
Results were twofold. First, across five anatomic areas--head, cervical spine, chest, abdomen/pelvis, and thoracolumbar spine--the in-field assessments based on injury mechanism or paramedic scene concerns had low overall diagnostic accuracy compared to CT scan. Second, these assessments were insufficient to constitute a reliable pre-hospital triage rule.

Conclusions
Our study suggests that paramedic assessment alone cannot be used to redirect patients away from level one trauma centers or there is considerable risk that significant injuries could be missed.
ROLE OF CIGARETTE AND COFFEE USE IN THE DEVELOPMENT OF ALCOHOLISM IN MEN AND WOMEN

Michael S. Reich, Mary S. Dietrich, Peter R. Martin.

Objectives
The proportion of recovering alcoholics who use cigarettes and coffee, in addition to the quantity of these psychoactive substances consumed, is greater than in the general population. However, there is little research examining possible roles for cigarettes and coffee in the etiology of alcoholism. Our research investigates the ontogeny of alcohol, cigarette, and coffee onset in the development and severity of alcohol dependence in recovering alcoholics.

Methods
Adult volunteers from all Nashville, English-speaking, open (to the public)-AA meetings (n=289 [126 women], completion rate=94.1%) were provided a Lifetime Drinking History modified for lifetime alcohol, cigarettes, and coffee consumption.

Results
Age (years) of first use of alcohol, cigarettes, and coffee were 15.4 (IQR: 13.0-18.0), 16.7 (IQR: 13.0-18.5), and 18.5 (IQR: 14.0-23.5), respectively. No gender differences were detected in the onset of alcohol or cigarette use (p>0.05); men started drinking coffee before women (p=0.034). In subjects who used all three substances, consumption of alcohol preceded cigarettes by 1.7 years (p<0.001) and coffee by 4.0 years (p<0.001); cigarettes preceded coffee by 2.3 years (p<0.001); gender effects did not alter this pattern. Men drank significantly more lifetime drinks and their drinking intensity was greater than that of women (both p<0.001).

Conclusions
Recovering alcoholic men and women initiated regular alcohol consumption prior to cigarette smoking and coffee drinking. These findings challenge the gateway role of both substances in future alcohol consumption, particularly in those who ultimately develop alcohol dependence, as the later consumed substance cannot be viewed to precipitate onset of the former. In light of the popularity of these substances and their differing psychopharmacological effects, further research is warranted investigating the effects of cigarettes and coffee on alcoholism.
ROUTINE COMPLETION CORONARY ANGIOGRAPHY AND THE RATE OF PERIOPERATIVE MI: DOES IT IMPROVE CLINICAL OUTCOME?

Jacob Elliott Schaff BA, Marzia Leacche MD, Ramanan Umakanthan MD, Nataliya V. Solenkova MD, David X. Zhao MD, John G. Byrne MD.

Objectives
A serious complication of coronary artery bypass surgery (CABG) is graft failure. When this occurs intraoperatively, it can contribute to perioperative myocardial infarction (MI). Intraoperative coronary angiography is considered the “gold standard” for assessment of graft patency; if a defect is found, it can be repaired immediately without having to return to the operating room at a later time.

The aim of this project was to see if routine completion coronary angiography decreases the rate of perioperative MI and improves clinical outcome.

Methods
This was a retrospective study between April 2005 and April 2006. During this period 199 patients underwent CABG followed by intraoperative routine completion angiogram and 126 patients underwent standard CABG with no confirmational imaging.

Results
Among the 438 imaged grafts, 61 (14%) angiographic defects were detected. Defects were repaired with either a minor adjustment of the graft (n=20, 4.5%) or with intraoperative percutaneous intervention or surgical revision (n=41, 9.5%). In comparison with patients who underwent standard CABG, those who underwent CABG followed by angiogram had no difference in rate of perioperative MI (1% vs. 2%, p=0.652) and in-hospital mortality (2% vs. 3%, p=0.710).

Conclusions
Routine completion angiography detected 14% of grafts with significant angiographic defects. No differences were found in the rate of symptomatic perioperative MI between the two groups. However, “silent ischemia” in patients with occluded grafts was not taken into account. It expected that follow-up routine coronary angiography performed at 12-18 months after surgery will show a difference in graft patency rate, especially in the subset of the population experiencing silent ischemia.
OBJECTIVE TREATMENT OF PARTIAL ACL TEARS

Michelle Shepard, BA, Joseph P. DeAngelis, MD, Warren R. Dunn, MD, MPH, and Kurt P. Spindler, MD

Objectives
To characterize the natural history of partial tears of the anterior cruciate ligament (ACL) in a highly active population.

Methods
From 2002 – 2007, patients with a partial ACL tear identified at surgery were deemed candidates for conservative treatment if they had 1) a solid endpoint on Lachman (2-4 mm side-to-side difference), 2) less than full pivot shift (less than one grade difference side-to-side), and 3) 50% of ACL fibers intact in normal anatomic configuration on arthroscopic examination. These patients were evaluated arthroscopically but did not undergo ACL reconstruction. All patients meeting these criteria were identified and contacted to determine if they had progressed to a complete ACL tear requiring ACL reconstruction.

Results
Of the 36 patients with a partial ACL tear, 33 (92%) were contacted at an average of 42 months (median 37, SD 21) from presentation. Only 2 of 33 patients (6%; 95% CI, 2% – 20%) required ACL reconstruction.

Conclusions
Short-term results suggest that there may be a subgroup of patients with partial ACL tears that do not require reconstruction. The proportion requiring subsequent ACL reconstruction is similar to that of revision surgery for primary ACL reconstruction. The rate of progression is similar to the incidence of ACL tears in the general population.

Table 1: Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>No ACL Reconstruction</th>
<th>ACL Reconstruction</th>
<th>Combined</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N = 34</td>
<td>N = 2</td>
<td>N = 36</td>
</tr>
<tr>
<td>Marx Activity Level</td>
<td>34</td>
<td>12.0 (9.7 ± 6.2)</td>
<td>16.0 (16.0 ± 0.0)</td>
<td>12.0 (16.0 ± 6.1)</td>
</tr>
<tr>
<td>Age</td>
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<td>36.0 (28.5 ± 5.4)</td>
<td>17.50 (17.5 ± 0.7)</td>
<td>28.00 (16.2 ± 9.47)</td>
</tr>
<tr>
<td>F/u Time</td>
<td>36</td>
<td>37.0 (42±21)</td>
<td>40.5 (40±30)</td>
<td>36.0 (41±22)</td>
</tr>
<tr>
<td>Sex: Female</td>
<td>36</td>
<td>29% (11/4)</td>
<td>50% (4)</td>
<td>30% (11/37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>71% (23/33)</td>
<td>50% (4)</td>
<td>70% (23/33)</td>
</tr>
</tbody>
</table>

a, b, c represent the lower quartile a, the median b, and the upper quartile c for continuous variables. x ± s represents X ± 1 SD.
N is the number of non-missing values.
DOES INITIAL HYPOTHERMIA PREDICT POOR OUTCOME AMONGST PEDIATRIC TRAUMA VICTIMS?

Jennifer Sundberg, MD, Thomas Abramo, MD, Cristina Estrada, MD

Background
Adult trauma patients (pts) who are hypothermic upon arrival to the emergency department (ED) have higher mortality rates. Few studies have assessed outcome of hypothermic pediatric trauma pts.

Objective
Is hypothermia an independent risk factor that predicts worse outcome among pediatric trauma patients?

Methods
A retrospective chart review of pediatric level one-trauma pts from September 2006 to March 2008 was conducted. Pts were included if a temperature (temps) was recorded within 30 minutes of arrival to the ED. Hypothermia was defined as a temp of \( \leq 95^\circ F \).

Results
Of the 226 level one trauma pts who presented to the PED during this time, 36 pts were excluded due to absent temp or temp recorded greater than 30 minutes after arrival. Analysis for pts' initial temp at the referral hospital was unsuccessful (< 30% recorded). Twenty one pts (11%) died. Median age was 8yrs (IQR 4-12.8yrs). Twenty two pts (11%) were hypothermic (range 88.1-95^\circ F). Mode of transport: ground 33%, air 67%. Head CT scans were performed on 160 pts (84%). Survival status by temp: alive (n=169) temp=97.9^\circ F\pm 1.7^\circ F, death (n=21) temp=94.9^\circ F\pm 3.2^\circ F.

Odds of death for a hypothermic pt were 9.2 times the odds of normothermic pt adjusting for season of year (95% CI=(3.22, 26.22), \( P < 0.0001 \)). Odds of death for a hypothermic pt were 8.7 times the odds of a normothermic pt adjusting for mode of transport (ground versus air), 95% CI= 3.1, 24.6, \( P < 0.0001 \).

Sixty one pts (32%) had positive findings on Head CT (temperature 97.1^\circ F, IQR 95.4 to 98.4). There was a moderate association between hypothermia and positive (intracranial pathology) Head CT (OR=2.4, 95% CI=(0.9,6), \( P =0.07 \)).

Conclusions
Hypothermic pediatric trauma pts have a higher mortality risk than those who are euthermic and may have a higher incidence of abnormal Head CT.
MEHARRY-VANDERBILT ALLIANCE REVOLUTION IN HEALTH CARE: ELIMINATING HEALTH CARE DISPARITIES IN CARDIOVASCULAR DISEASE IN DAVIDSON COUNTY.

Modele Ogunniyi, Clare Murphy, Kimberli Taylor-Clarke, Uchechukwu Sampson, Henry Okafor, Lavenia Crutcher, Mary Bufwack, Keith Junior, Alfred Callahan, Russell Rothman, Thomas DiSalvo, Michael Floyd, Andre Churchwell, Douglas Sawyer, on behalf of the MVA Revolution in Cardiovascular Healthcare Team

Background
Cardiovascular disease (CVD) remains the leading cause of mortality in Davidson County. The mostly affected population subgroups include ethnic minorities and persons of low socioeconomic status despite no known differences in atherogenesis in these populations. Current programs of preventive care appear inefficient given both high prevalence of disease and disparity of its burden in Middle Tennessee.

Objectives
The goal is to develop a set of interwoven, innovative models focused on preventing and optimizing treatment of CVD, in primary and secondary disease populations with a special emphasis on heart failure (HF).

Methods
In an effort to eliminate cardiovascular health disparities within Davidson County, our multi-disciplinary team will identify patients who are at highest risk of developing HF and use our novel, systematic program for prevention delivery. This program is focused on patients, providers and community centered strategies.

For those persons identified with HF, our program will coordinate their care with both hospital and specialty clinic emphasis. The use of educational tools for healthcare providers, ancillary personnel and families will be incorporated to improve late stage outcomes.

Conclusion
We anticipate that this multi-facetted approach will improve the health of the underserved population of Davidson County and may be shown to reduce the overall cost of care. In addition, the work supported by this proposal will lead efforts for extramural funding for long-term projects that will positively impact the health of our community by proving sustainability.
USING EMS ON THE SCENE TO ACTIVATE THE CARDIAC CATHETERIZATION LABORATORY IN STEMI PATIENTS

Eric Thomassee, MD, Robert L. Huang MD MPH, Carol Scott RN, Robin Steaban, RN, Joseph Fredi, MD

Background
The ACC/AHA Guidelines recommend primary percutaneous coronary intervention (PCI) in acute ST elevation myocardial infarction (STEMI) patients to be completed within 90 min from presentation to the healthcare system. However, patients transferred from other acute care hospitals are often excluded from national quality measures. Recent data suggests that the majority (72.3%) of STEMI patients transferred for primary PCI have reperfusion times greater than 120 min.

Methods
We developed an acute MI network that grants outside hospital ED physicians direct access to our helicopter system and cardiologist on-call. This system pages all catheterization lab personnel, reserves a CCU bed, and launches a near-by helicopter facilitating transfer from outside hospitals for STEMI patients to receive primary PCI. Beyond our network, we have piloted a program where EMS can activate the catheterization lab through our network, empowering EMS personnel to diagnose and triage STEMI patients. We hypothesize this will decrease reperfusion times as our preliminary data suggests that the majority of delays occur at the outside hospital. We collected data on these “Scene” STEMI patients who have been transferred directly from the field to the catheterization lab. Data will be presented in a case series.

Results
From 12/07 to 12/08, 8 STEMI patients were transferred by EMS directly to our medical center for primary PCI. Distance from the scene to our medical center ranged from 40 to 75 nautical miles (avg 54 miles). Time from EMS presentation to reperfusion ranged from 102 to 151 min (avg 119 min). Median time from acute care facility presentation to reperfusion at Vanderbilt Medical Center was 144 min (n=103). Our “Scene” STEMI patients had a median time of 115 min, a difference of 29 min. To date, there have been no false activations of our STEMI network through EMS.

Conclusions
Eight “Scene” STEMI patients were diagnosed and triaged to our center for completion of primary PCI. Our data shows feasibility of an EMS-activated STEMI network and suggests improvement in reperfusion times with its use. Systems of care may be improved by focusing on education of EMS on diagnosis of STEMI and directly transporting these patients for primary PCI.
A PHASE I STUDY OF CETUXIMAB IN COMBINATION WITH GEMCITABINE AND RADIATION FOR LOCALLY ADVANCED PANCREATIC CANCER

C. Jillian Tsai, Ph.D., A. Bapsi Chakravarthy, M.D., Jordan D. Berlin, M.D., A. Craig Lockhart, M.D., Emily Chan, M.D., Alexander Parikh, M.D., Valerie Kordowski, Nipun Merchant, M.D.

Objectives
Cetuximab (C225, Erbitux) is a chimeric mouse-human monoclonal antibody against the epidermal growth factor receptor (EGFR) extracellular domain. The primary goal of this phase I study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of gemcitabine when combined with cetuximab/radiation in patients with locally advanced pancreatic cancer.

Methods
Patients with locally unresectable adenocarcinoma of the pancreas were enrolled on study. Cetuximab was delivered as a loading dose of 400 mg/m2 (week 1, day 1), followed by weekly infusions of 250 mg/m2 (weeks 2-7). All patients received radiation of 5040 cGy starting on day 8. Gemcitabine was given weekly starting on day 8 for 6 weeks. The starting dose of gemcitabine was 200 mg/m2 with planned dose escalations of 100 mg/m2 increments at each dose level.

Results
Nine patients were enrolled on study. One patient was taken off study due to declining performance status prior to receiving any therapy. Two patients developed a grade 4 allergic reaction to cetuximab and were taken off study. Another patient developed elevated liver function tests and a stroke the week following his loading dose of cetuximab. Three of the remaining five patients treated on dose level 1 developed grade 3 or 4 toxicities and therefore no further dose escalations were planned. Grade 3 toxicities included nausea, vomiting, ileus and pneumonitis. One patient developed grade 4 diarrhea.

Conclusions
The combination of cetuximab, gemcitabine and radiation resulted in significant toxicity. A recommended phase II dose could not be determined. Further investigation with this combination needs to be approached with caution.

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A PHASE II TRIAL OF NEOADJUVANT DOCETAXEL FOR WOMEN WITH
LOCALLY-ADVANCED BREAST CANCER

C. Jillian Tsai, Ph.D., Ingrid A. Mayer, M.D., Josh A. Bauer, Ph.D., Ingrid Meszoely,
M.D., Melinda Sanders, M.D., Mark C. Kelley, M.D., Graciela Olivares, M.D., Julie
Means-Powell, M.D., Ana M. Grau, M.D., David H. Johnson, M.D., R. Daniel
Beauchamp, M.D., Jennifer A. Pietenpol, Ph.D., A. Bapsi Chakravarthy, M.D.

Objectives
We conducted a phase II study to determine the safety and pathologic response rates
of neoadjuvant dose-dense docetaxel therapy in patients with stage II/III breast cancer.

Methods
Patients with high-risk, stage II/III breast cancer were treated with 4 cycles of do-
cetaxel 100 mg/m2 every 2 weeks with growth factor support. Due to significant grade
3 toxicities in the first 20 patients, the dose was reduced to 75 mg/m2 for the remain-
ing 14 patients. Pre- and post-docetaxel core biopsies were obtained. At completion of
docetaxel, patients had the option to proceed with either definitive surgery or receive 4
cycles of Adriamycin/Cyclophosphamide (AC) if further downsizing of tumor was
indicated by the treating physician. Additional adjuvant chemotherapy, radiation, en-
docrine or trastuzumab therapy was administered at the discretion of the treating phy-
sician.

Results
All 34 patients completed 4 cycles of docetaxel, and of these, 7 patients received
neoadjuvant AC in addition to docetaxel. Five patients (14.7%) achieved pathologic
complete response (3 of those received neoadjuvant AC in addition to docetaxel). Of
the first 20 patients that received 100 mg/m2, 8 (40%) required 25% dose reduction
for at least 1 cycle due to toxicities and 5 (25%) had treatment delays. Two of the 14
(14%) patients who received planned 75mg/m2 docetaxel had additional 25% dose
reduction and 6 (43%) had treatment delays. There were no grade 4 docetaxel-related
toxicities. Grade 3 toxicities were more common in patients receiving 100mg/m2 do-
cetaxel than in those who had 75mg/m2 (13 [65%] vs. 5 [35.7%], respectively). The
most common grade 3 toxicities were musculoskeletal (myalgia), constitutional
(fatigue), dermatological (rash and hand-foot syndrome) and infection. At 31.5 month
follow-up, 94% of the patients are alive without evidence of disease.

Conclusions
Neoadjuvant dose-dense docetaxel at 100 mg/m2 resulted in significant toxicities that
required initial dose reduction to 75 mg/m2. With reduced doses, treatment was feasi-
ble and well tolerated. The observed rate of pathologic complete response after dose-
dense docetaxel was not superior to previously reported studies with single agent pa-
clitaxel.
ADHERENCE TO PROPHYLACTIC ANTIBIOTIC GUIDELINES AMONG TENNESSEE MEDICAID INFANTS WITH SICKLE CELL DISEASE


Objectives
Infants with sickle cell disease (SCD) have a 30- to 100-fold increased rate of pneumococcal infection compared with the general population. Low rates of adherence to prophylactic antibiotic guidelines have been described in older children with SCD, but little is known about initiation of prophylactic antibiotics in infancy, a period of great vulnerability. We sought to describe adherence to guidelines for initiation of prophylactic antibiotics among a cohort of Tennessee Medicaid infants with SCD and to identify risk factors for non-adherence.

Methods
We conducted a retrospective cohort study using Tennessee Medicaid claims and birth certificates. Cohort infants were born between 1997-2006, were enrolled in TennCare continuously for the first 6 months of life, had a Tennessee birth certificate, and had an ICD-9 claim for SCD (one inpatient or two outpatient claims). Using pharmacy claims, we classified infants according to whether they filled a prophylactic antibiotic prescription within the first 12 weeks of life. Infants were also classified according to risk factors previously associated with failure to receive preventive care: lower maternal age, single maternal marital status, lower maternal education, distance from medical center, and economic status.

Results
Of 407 infants in the cohort, 53% were male, 28% were born to mothers younger than 20, 76% to mothers with ≤ 12 years of education, and 83% to unmarried mothers.

Overall, 60% of cohort infants failed to fill the first prophylactic antibiotic prescription within 12 weeks. Having four or more risk factors increased the risk of non-adherence. Among infants with 4 or 5 risk factors, 72% failed to start prophylaxis within the first 12 weeks of life, compared to 60% and 48% of infants with 2-3 and 1-2 risk factors, respectively (p=0.014).

Conclusions
Despite specific care guidelines and literature supporting early prophylaxis, many Tennessee infants with SCD did not initiate prophylactic antibiotics within the recommended interval. This finding highlights the need for improved provision of prophylactic therapies in this vulnerable population.