48th Annual Scientific Research Symposium

Friday, August 4, 2016
Great hall
The Mary Duke Biddle Trent Semans Center for Health Education
Άξιον ωφελείν τοὺς αλγούντας

"Be worthy to serve the suffering"
Sally A. Kornbluth, PhD
Vice Dean of Research, Duke School of Medicine
Provost, Duke University
Jo Rae Wright University Professor

Friday, August 4, 2017
The Mary Duke Biddle Trent Semans Center for Health Education
Great Hall

7:30 - 8:00 AM  Platform Presentation Setup
Breakfast – Served in the Great Hall Lobby, level 0

8:00 - 8:30 AM  Keynote Address:  Sally A. Kornbluth, PhD

8:40- 11:00 AM  Platform Presentations

11:00 - 12:45 PM  Poster Presentations

12:45 - 1:30 PM  Pick up lunch – Learning Hall, level 2
RETURN TO THE GREAT HALL FOR 1:30 PM EVENTS

1:30 – 2:15PM  Updates to the Curriculum
Edward Buckley, M.D., Vice Dean for Education
Colleen O'Connor Grochowski, Ph.D., Associate Dean for Curricular Affairs

2:15 - 2:45PM  Valentine Esposito, Davison Council President

2:45 – 3:00 PM  Presentation of Awards

3:00 PM  Adjourn
The Duke ΑΩΑ Chapter would like to thank the following for their participation in today’s Symposium:

**Platform Judges**

Sally A. Kornbluth, PhD  
Vice Dean of Research, Duke School of Medicine  
Provost, Duke University  
Jo Rae Wright University Professor

Edward Buckley, M.D.  
Professor of Ophthalmology; James Pitzer Gills, III, M.D. and Joy Gills Professor of Ophthalmology in the School of Medicine; Professor in Pediatrics;  
Vice Dean for Education; Chair, Department of Ophthalmology

Victor J. Nadler, Ph.D.  
Professor Emeritus of Pharmacology & Cancer Biology,  
Professor of Neurobiology

Daniel Laskowitz, M.D., M.H.S.  
Professor and Vice Chair of Neurology; Professor of Anesthesiology & Neurobiology; Director, Neurovascular Laboratories

Philip Rosoff, M.D., M.A.  
Professor of Pediatrics (Hematology-Oncology), Professor of Medicine;  
Director of Clinical Ethics, Duke University Hospital

**Poster Judges**

Andolsek, Kathryn, M.D., MPH, Associate Director, Graduate Medical Education; Community and Family Medicine  
Bennett, Ellen, Ph.D, Assistant Professor in Neurology  
Blitzblau, Rachel, M.D., Ph.D, Butler Harris Assistant Professor in Radiation Oncology  
Blobe, Gerald, M.D., Ph.D, Professor of Medicine, Professor of Pharmacology and Cancer Biology, Member of Duke Cancer Institute  
Bowes-Rickman, Catherine, Ph.D, Associate Professor of Ophthalmology  
Cheifetz, Ira, M.D. FCCM, FAARC, Professor of Pediatrics, Professor in Anesthesiology, Chief, Division of Pediatric Critical Care Medicine  
Chiba-Falek, Ornit, Ph.D., Assistant Professor of Neurology, Department of Neurology, Bryan Alzheimer's Disease Research Center and Duke Institute for Genome Sciences & Policy  
Crawford, Lawrence, M.D., Associate Professor of Medicine  
Dupre, Matthew, Ph.D., Associate Professor in Community and Family Medicine  
Feng, Liping, M.D., Assistant Professor of Obstetrics and Gynecology  
Foster, Mary, M.D., Associate Professor of Medicine, Member of the Duke Cancer Institute  
Gbadejesin, Rasheed, M.D., MBBS, Associate Professor of Pediatrics and Nephrology, Faculty of Member of Duke Molecular Physiology Institute  
Grabner, Alex, M.D., Medical Instructor in the Department of Medicine  
Hobson-Webb, Lisa, M.D., Associate Professor of Neurology  
Holl, Eda, Ph.D, Assistant Professor of Surgery
Holley, Christopher, M.D., Ph.D., Assistant Professor of Medicine - Cardiology
Holmes, Megan, Ph.D, Medical Instructor in Physician Assistant Program
James, Michael, M.D., Associate Professor of Anesthesiology
Limkakeng, Alexander, M.D., M.H.S., Associate Professor of Surgery
Lin, Shu, M.D., Ph.D., Associate Professor of Cardiovascular and Thoracic Surgery
Lo, Joseph, Ph.D, Professor of Radiology
McNulty, Amy, Ph.D., Assistant Professor of Orthopaedic Surgery, Assistant Professor of Pathology
Michener, James Lloyd, M.D., DTMI - Duke Center for Community Research (DCCR); Professor of Community and Family Medicine; Clinical Professor, School of Nursing; Chair, Department of Community and Family Medicine
Nadler, Victor J., Ph.D., Professor of Pharmacology & Cancer Biology, Department of Neurobiology
Nair, Smita, Ph.D., Professor in Surgery, Professor in Pathology, Member of the Duke Cancer Institute
Oeffinger, Kevin, M.D., Instructor in Department of Medicine, Member of the Duke Cancer Institute
Perkins, Jennifer, M.D., Associate Professor of Medicine, Endocrinology
Permar, Sallie, M.D., Ph.D., Assistant Professor of Pediatrics- Infectious Diseases, Associate Professor in Immunology, Associate Professor in Molecular Genetics and Microbiology, Member of Duke Human Vaccine Institute, Affiliate, Duke Global Health Institute
Rao, P. Vasantha, Ph.D., Professor Ophthalmology, Professor in Pharmacology and Cancer Biology
Reed, Ann, M.D., William Cleland Professor of Pediatrics, Chair, Department of Pediatrics
Rosdahl, Julilia, PhD, M.D., Assistant Professor of Ophthalmology
Salama, Joseph, M.D., Associate Professor and Chief, Radiation Oncology Clinical Services, Durham VA Medical Center
Shenoy, Sudha, Ph.D., Associate Professor of Medicine – Cardiology, Associate Professor in Cell Biology, Member of the Duke Cancer Institute
Silberberg, Mina, Ph.D., Associate Professor in Community and Family Medicine
Sosa, Julie, M.D., Professor of Surgery, Professor of Medicine – Medical Oncology, Member of the Duke Clinical Research Institute, Member of the Duke Cancer Institute
Sparks, Matthew, M.D., Assistant Professor of Medicine - Nephrology
St. Clair Russell, Jennifer, Ph.D, Medical Instructor in Department of Medicine
Stafford-Smith, Mark, M.D., Professor of Anesthesiology
Thielman, Nathan, M.D., Professor of Medicine, Research Professor of Global Health, Professor of Pathology
Thompson, Eric, M.D., Assistant Professor at Duke Pediatric Neurosurgery
Tucci, Debara, M.D., Professor of Surgery, Head and Neck Surgery & Communication Sciences
Visco, Anthony, M.D., Professor of Obstetrics and Gynecology
Wang, Virginia, Ph.D., Associate Professor in Medicine
Wong, Charlene, M.D., Assistant Professor of Pediatrics, Member in the Duke Clinical Research Institute

**Special Thanks**
Mr. E. Arthur Palumbo, a 1949 Duke University graduate, established The Palumbo Family Medical Scholarship which provides a full-tuition scholarship for the fourth year of medical school and will be awarded today. Mr. Palumbo is a great friend of Duke Medicine who has also provided major funding to Duke Children’s Hospital, and who also established The Leonard Palumbo, Jr., MD Faculty Achievement Award in memory of his brother – a Duke University School of Medicine alumnus (MD 1944) and former Duke Obstetrics and Gynecology faculty member. The award is given annually to one or more Duke School of Medicine faculty members who best exemplify the qualities of compassionate patient care and dedication to teaching and mentoring young physicians that his late brother embodied.
PLATFORM PRESENTATIONS
PLATFOM PRESENTATIONS SCHEDULE

8:40 – Kristian Becker
MicroRNA profiling in non-ST Elevated Coronary Artery Syndrome Highlights Genomic Associations with Serial Platelet Reactivity Measurements
Mentor: Svati H. Shah, MD, MHS
Human Genetics and Genomics Study Program, Rasheed Gbadegesin, MBBS, MD, Director

8:52--Philip Tseng
How Much Does This ‘Bill’ Cost? Provider Billing and Insurance-Related Costs in the United States Health Care System
Mentor: Kevin Schulman, MD
Dual Degree, MBA Study Program, Jennifer Perkins, MD, MBA, Director

9:04 – Jennifer Chien
Implantable Oxygen Biosensor Reveals Post-Ischemia Tissue Reactive Hyperoxia
Mentor: Bruce Klitzman, PhD
Biomedical Engineering and Surgery Study Program, Bruce Klitzman, PhD, Director

9:16 – Momodou Jammeh
ALK4 Loss Drives Epithelial-Mesenchymal Transition to Promote Pancreatic Ductal Adenocarcinoma Progression
Mentor: Gerald Blobe, MD, PhD
Molecular Medicine Study Program, David Hsu, MD, PhD, Director

9:28--Jessica Hoffman
An integrated clinic-community partnership for child obesity treatment: A randomized pilot trial
Mentor: Sarah Armstrong, MD
Primary Care Leadership Track, Anh Tran, PhD, MPH, Director

9:40 – Xiaojie "Zoe", Zhang
Exercise Blunts Tumor Growth via Differential Immune System Modulation
Mentor: Mark W. Dewhirst, DVM, PhD
Radiation, Radiation Oncology and Medical Physics Study Program, Joseph Lo, PhD, Director

9:52 – Tolulope Teniola
Infertility and Ovarian Cancer risk in African American Women
Mentor: Patricia Moorman, PhD, MPHS
Clinical Research Study Program, Vivian Chu, MD, Director
10:04 – Howard Lee
Correlation of Functional Lung Heterogeneity and Dosimetry to Radiation Pneumonitis using Perfusion SPECT/CT and FDG PET/CT Imaging
Mentor: Ramesh Rengan, MD, PhD, University of Washington Department of Radiation Oncology Radiation, Radiation Oncology and Medical Physics Study Program, Joseph Lo, PhD, Director

10:16 – Jerry Lee
Directing B and T Cell Differentiation for Hematopoietic Stem Cell Therapy
Mentor: George Q. Daley
Molecular Medicine Study Program, David Hsu, MD, PhD, Director

10:28 – Mara Storto
Cav1.2 gain-of-function mutation causes aortic valve stenosis
Mentor: Geoffrey Pitt, MD, PhD, Weill Cornell Medicine, New York Cardiovascular Research Study Program, Neil Freedman, MD, Director

10:40 – Gary Sulioti
Long-Term Changes in White Matter Microstructure during Recovery from mTBI in a Civilian Population
Mentor: Pratik Mukherjee, MD PhD, University of California, San Francisco Radiation, Radiation Oncology and Medical Physics Study Program, Joseph Lo, PhD, Director
MicroRNA Profiling in non-ST Elevated Coronary Artery Syndrome Highlights Genomic Associations with Serial Platelet Reactivity Measurements

Kristian C. Becker, Lydia Kwee, Megan L. Neely, Elizabeth Burns, Joseph A. Jakubowski, Keith A.A. Fox, Harvey White, Simon G. Gregory, Paul W. Armstrong, Leonardo de Pinto Carvalho, E. Magnus Ohman, Matthew Roe, Svati H. Shah, Mark Y. Chan

The Eugene A. Stead Jr. MD Research Scholarship

Background: Platelet Reactivity (PR) is a known contributor to acute coronary syndrome (ACS) associated morbidity and mortality, including unstable angina (UA) and nSTE-MI. Recent studies have highlighted the association between circulating microRNA levels and PR. To understand inter-individual PR heterogeneity and its associated cardiovascular risk, we assessed microRNA and PR values in three distinct ACS cohorts; a case-control cohort, a large-scale ACS cohort and an independent validation cohort.

Methods: Whole-blood miRNA sequencing (miRNA-seq) was performed in a case-control NSTE-ACS population with and without recurrent cardiovascular events (N=149). Targeted Real-time polymerase chain reaction (rt-PCR) was performed for 41 targeted miRNAs in serial plasma samples at three time points; baseline, 30 days and six months (N=712). Finally, miRNA species significantly associated with PR were validated using an independent ACS cohort from Singapore (N=96).

Results: Eighteen miRNA species were associated with PR by miRNA-seq in the whole blood case-control cohort (p = 0.004 to 0.05, Log2 fold-change per count: -0.09 to 0.09). Three miRNAs were associated with PR by rt-PCR in the large serial plasma cohort: miR-126-5p (combined 30 day and six month GEE analyses, Beta: -0.08, p=0.03, 30 day time-point LR, Beta: -0.13, p=0.01); miR-574-3p (GEE, Beta: -0.1, p=0.007 and six month time-point LR, Beta: -0.12, p=0.02) and Let-7d-3p (GEE, Beta: -0.08, p=0.03 and six month time-point LR, Beta: -0.15, p=0.005). Of the miRNA significantly associated with PR by miRNA-Seq and rt-PCR, Let-7a-5p and miR-93-3p validated with directional consistency in the Singapore plasma validation cohort.

Conclusions: In this study, the largest study of serial miRNA and PR profiling in nSTE-ACS patients to date, we identified two novel miRNAs, Let-7a-5p and miR-93-3p, that associate with PR. Our results highlight new potential biologic pathways previously unidentified in PR, and suggest that miRNA and PR associations in a post-ACS population may be time-dependent, changing over the first six months following an nSTE-ACS event.
**How Much Does This ‘Bill’ Cost? Provider Billing and Insurance-Related Costs in the United States Health Care System**

Phillip Tseng, MBA, MEd, Robert Kaplan, PhD, Barak Richman, JD, PhD, Mahek Shah, MD, Kevin Schulman, MD, MBA

**Background:** Administrative costs in U.S. healthcare are estimated to represent between 25.3 and 31.0 percent of total healthcare expenditures, a proportion that is twice that of Canada and significantly greater than all other OECD nations where such costs have been comparatively studied. Each percentage of administrative cost at a national level currently represents $26 billion, or resources sufficient to provide healthcare for more than 2.5 million Americans. Two-thirds of this administrative burden in the U.S. has been attributed to billing and insurance-related (BIR) functions, which in some provider settings cost nearly four times more than corresponding costs in Canada. Studies to date have used top-down allocations of aggregate data to estimate BIR costs, providing limited clarity on the specific sources of these high costs. We provide more granular detail by using a bottom-up costing approach, time-driven activity-based costing (TDABC), in a single academic health system located in a North Carolina suburb.

**Methods:** We first constructed a process map that charts the path followed by an individual bill through the entire revenue cycle at the Duke Patient Revenue Management Organization (PRMO). We then calculated a time-driven cost for each major activity that such a bill encounters, and finally summed the costs of each activity to calculate the total cost of processing an insurance claim. Overhead costs were allocated according to the average labor time necessary for BIR processing. Total costs were obtained for five types of patient encounters: primary care visit, discharged emergency visit, ambulatory surgery, inpatient surgery, and general medicine inpatient stay.

**Results:** Total cost of provider-side BIR activities range from $20 for a primary care visit to $183 for an inpatient surgical procedure. For primary care, provider BIR cost is 14 percent of revenue and represents an annual cost of $96,440 per primary care physician. These costs could not be attributed to significantly wasteful processes within the health system studied. Future TDABC studies that consider both payer and provider perspectives would likely produce total BIR costs more than twice these figures.

**Conclusions:** These costs appear to arise not from inefficiency on the part of provider organizations, but from the broader administrative complexity in the current U.S. multi-payer reimbursement architecture. There could be significant economic benefits from standardizing and simplifying this system.
Implantable Oxygen Biosensor Reveals Post-Ischemia Tissue Reactive Hyperoxia

Jennifer S. Chien, BSE, Mahmoud Mohammed, BE, Hysem Eldik, BS, Mohamed M. Ibrahim, MD, Scott Nichols, PhD, Natalie Wisniewski, PhD, Bruce Klitzman, PhD

**Background:** This study utilized an implantable biosensor to measure tissue oxygenation before, during, and after a transient ischemic insult. The purpose of this study was to use implantable O₂ sensors to quantify local O₂ content following ischemic challenges and perfusion restoration.

**Methods:** All animals were treated according to approved IACUC protocols. First, rats were subjected to unilateral femoral artery and vein ligation and received bilateral biosensors in the hind limbs. The biosensors were composed of a porphyrin embedded into a porous poly-hydroxyethylmethacrylate (pHEMA) scaffold and were injected through an 18-gauge needle into the subcutis. The biosensor’s phosphorescence lifetime changed inversely with O₂ concentration. Near infrared spectroscopy (NIR) was also used to quantify percent O₂ saturation of hemoglobin at the tissue level. Laser Doppler flowmetry was used to quantify blood flow. On post-operative days 28 and 84, the rats underwent a series of systemic hypoxic challenges as well as bilateral hind limb tourniquet application. Response magnitudes, response times and normalized changes were calculated for comparison between techniques. Statistical significance was assessed using ANOVA and two-sample paired t-test at p-value ≤ 0.05.

**Results:** Laser Doppler flowmetry confirmed a reactive hyperemia following tourniquet release. In addition, both the phosphorescence lifetime biosensor and NIR methods suggested that the tissue O₂ content temporarily but significantly exceeded baseline following tourniquet release (p<0.05). We term this phenomenon reactive hyperoxia. This suggests that the O₂ supply transiently exceeds oxygen consumption. Even though tissue O₂ consumption was expected to be elevated following ischemia to repay the O₂ debt developed during occlusion, the elevated O₂ content indicates that the increased consumption is met with an even greater elevated O₂ supply. The NIR spectroscopy and phosphorescence lifetime data are consistent. The phosphorescence lifetime biosensor also demonstrates a more prominent response magnitude in general and a faster response over time (71 secs vs. 143 secs in NIR; p = 0.0053), suggesting that the sensing elements may have gained greater proximity to the blood supply via vascular ingrowth through the porous pHEMA scaffold.

**Conclusions:** The implantable phosphorescence lifetime biosensor provided real time monitoring of tissue oxygenation, with a rapid and prominent response, excellent biocompatibility and highly localized measurements. Both the phosphorescence lifetime and NIR spectroscopy techniques demonstrated a reactive hyperoxia post ischemia. Direct assessment of tissue oxygenation may provide helpful diagnostic and prognostic information on transplant prognosis, wound healing, 3D scaffold design, ischemic brain tissue monitoring, and efficacy before, during and after interventions for tissue oxygenation or re-vascularization, such as grafting, stenting or bypass procedures.
ALK4 Loss Drives Epithelial-Mesenchymal Transition to Promote Pancreatic Ductal Adenocarcinoma Progression

Momodou L. Jammeh, Jian C. Chen, Gerard C. Blobe
Howard Hughes Medical Institution Fellowship

Background: Pancreatic ductal adenocarcinoma (PDAC) is a major leading cause of cancer mortality worldwide. Early invasion and high metastatic potential are hallmarks of PDAC but the underlying mechanisms are incompletely understood. Epithelial-mesenchymal-transition (EMT) is a conserved process that gives polarized epithelial cells the enhanced migratory and invasive properties of mesenchymal cells ultimately leading to metastasis. While transforming growth factor-β (TGF-β) signaling regulates proliferation in early development and embryogenesis, it is an established driver of the EMT process to promote cancer progression. A potential explanation for this dichotomous role of TGF-β in cancer is the loss activin-like receptor kinase 4 (ALK4), a serine/threonine kinase transmembrane receptor that mediates signals from TGF-β superfamily ligands. ALK4 expression is decreased in ~30% of pancreatic cancers and this loss correlates with advanced disease stage and poorer prognosis.

Methods: To investigate the role of ALK4 in PDAC progression, we silenced ALK4 in pancreatic cancer cell lines PANC1, MiaPACA and HPNE (shALK4) using a lentivirus stably expressing ALK4 shRNA. RT-PCR and biotinylation with immunoprecipitation and western blotting were used to confirm knockdown efficiency. Cell proliferation was evaluated with 3H thymidine incorporation assays and soft agar colony formation assays were used to model tumorigenicity. Transwell migration and Matrigel invasion assays were used to model these aspects of tumor biology in vitro. We orthotopically implanted luciferase expressing ALK4 silenced HPNE cells into athymic nude mice to assess the role of ALK4 in vivo. We also reviewed publically available datasets of ALK4 mRNA expression in clinical specimens to assess its effect on survival.

Results: We demonstrate that decreased ALK4 expression induces epithelial-mesenchymal transition (EMT) and promotes migration. Specifically, ALK4-silenced cells had decreased expression of epithelial markers E-cadherin and β-catenin, with upregulation of mesenchymal markers N-cadherin and vimentin. In vivo, orthotopic implantation of luciferase expressing shALK4-silenced HPNE cells resulted in significantly smaller primary tumor burden relative to shNTC HPNE implanted mice (0.5 g vs 1.5 g, P < 0.01). However, we observed a 3-fold increase in the incidence of mesenteric lymph node and liver metastasis in the shALK4 HPNE mice compared to shNTC. Histologic staining of harvested tissue revealed the upregulation of epithelial marker ZO-1 in shNTC HPNE tumors and higher mesenchymal marker vimentin expression in shALK4 HPNE tumors, suggesting that loss of ALK4 expression promoted EMT in vivo.

Conclusions: These data suggest that while loss of ALK4 decreases primary tumor growth, it facilitates the development of highly metastatic tumors through induction of EMT. Further investigation into the mechanisms underlying the aggressive tumor phenotype observed in low ALK4 expressing cells is warranted and may yield new therapeutic targets to improve patient outcomes.
An integrated clinic-community partnership for child obesity treatment: A randomized pilot trial

Jessica Hoffman, Leah Frerichs, PhD, Mary Story, PhD, RD, Jason Jones, CPRP, CPO, Kiah Gaskin, MSW, MPH, Annie Apple, Asheley Skinner, PhD, Sarah Armstrong, MD

The Obesity Society “Early Career Award”

Background: Effective treatment for child obesity remains elusive, and treatment guidelines are challenging to deliver in real-world clinical settings. Integration of clinical and community systems can provide both individualized and social supports for lifestyle modification, but little is known about the feasibility or effectiveness of this model. The purpose of this pilot trial is to evaluate the feasibility and effectiveness of an integrated healthcare partnership with Parks and Recreation in the treatment of child obesity. We hypothesize that the integrated model is more effective in improving BMI and child health behaviors, as compared to clinical treatment alone.

Methods: We conducted a randomized, controlled, non-blinded clinical trial with children (n=97) aged 5-11 with a BMI ≥ 95th percentile presenting to a pediatric weight management program for obesity treatment, and one parent. All subjects received standard care through the weight management program, including monthly visits with medical providers and dieticians. Intervention subjects were also invited to participate in a community-based wellness program at a local Parks and Recreation Center. Primary outcomes included change in child BMI at 6-months, and feasibility of the program in meeting recommended treatment hours. Secondary outcomes included change in health behaviors, fitness, and quality of life.

Results: We enrolled 97 participants and retained 70% at 6 months. Children were 53% female, 51% Black/African-American, and 34% Hispanic. Mean age was 9.1 years, and mean BMI z-score was 2.28. Parents were 87% female and 48% single, with a mean BMI of 34.6 kg/m². About one-fourth (23%) had a household income <$5000/year. Intervention subjects achieved, on average, 11.4 hours (range: 2-67.8; SD 15.3) of clinic-community treatment over 6 months, versus 4.4 hours (range: 2-9; SD 1.6) of clinical treatment achieved by control subjects. Barriers to participation in the community program included parent work schedules and transportation. Although we did not observe any between-group differences in child BMI z-score at 6 months, we observed statistically significant improvements among participants in the intervention group in waist circumference (+0.93cm vs. +4.92cm, 95% CI -0.01 to 7.97, P = 0.051), physical activity (+0.25 vs. -0.21 activity score, 95% CI -0.79 to -0.11, P = 0.010), and quality of life (+12.66 vs. +3.31, 95% CI -16.15 to -2.56, P = 0.008).

Conclusions: An integrated clinic-community model of child obesity treatment is feasible to deliver in a low-income and racially-diverse population. As compared with multidisciplinary treatment, the integrated model provides more treatment hours, improves physical activity, and increases quality of life. Parks and Recreation holds significant promise as a partner agency to deliver child obesity treatment. Future research should evaluate the implementation potential and the long-term effectiveness of the integrated model of obesity treatment.
Exercise Blunts Tumor Growth via Differential Immune System Modulation

Zhang X, Ashcraft KA, Rickard AG, Dewhirst MW
Howard Hughes Medical Institute

Background: Exercise as a mode of therapy has long been used in managing illnesses from diabetes to coronary artery disease. However, defining the role of exercise in cancer therapy has been limited. In our murine models of orthotopically implanted breast tumor 4T1-luc cells, exercise slowed tumor growth rates, reduced metastasis, and improved survival. Exercise reduced tumor hypoxia by up to 50%, normalized tumor vasculature (via CD31 staining) and improved tumor perfusion. Through improved oxygenation and enhanced drug delivery, we showed that exercise sensitizes tumor response to chemotherapy and radiation therapy (RT). Beyond the intuitive effects of reduced hypoxia, exercise modulation of tumor environment gives rise to the deeper, unexplored question of the role of the immune system in blunting tumorigenesis. It has been shown that immune cells are mobilized by exercise, but their activity is inversely related to hypoxic stress. Since exercise improves oxygenation, we hypothesize that exercise slows tumor growth via altered cytokine release and differential immune cell recruitment to the tumor site.

Methods: In our preliminary study, syngeneic BALB/c mice with mammary pad implants of 4T1-Luc tumors are split into voluntary wheel running and sedentary, no wheel groups. We further investigated whether exercise induced tumor immune response is transferable from immunocompetent exercised vs. sedentary donor mice to lymphodepleted recipients using an adoptive transfer method. Tumor growth, cytokine expression, and tumor infiltrating lymphocytes are measured.

Results: Our results reveal that exercise in tumor-bearing, immunocompetent Balb/c mice increased tumor infiltration by cytotoxic T cells: via flow cytometry, we detected a twofold infiltration by CD8+ cytotoxic T cells in the tumors of exercise mice compared to sedentary mice. This differential recruitment of immune cells combined with less hypoxia may contribute to greater immune surveillance. We have also found exercise reduced proinflammatory cytokines such as leptin by 20% compared with sedentary control mice. Moreover, when the ratio of the anti-inflammatory cytokine, adiponectin, to leptin is examined, exercise increased this ratio by 50%. In the adoptive transfer study, we established a radiation dose that is sufficient to deplete lymphocytes in recipient mice, without inducing whole body toxicity. Our preliminary results have shown tumor-bearing recipients of exercising donors’ lymphocytes demonstrated delayed tumor growth compared to recipients of lymphocytes from sedentary donors. Furthermore, via peripheral blood analyses, adoptively transferred exercise lymphocytes proliferated at a faster rate within the recipient mice compared to sedentary lymphocytes.

Conclusions: Our data suggests exercise induces both quantitative and functional potentiation of the anti-tumor immune response. This study offers insights into novel mechanisms underlying how a highly accessible mode of lifestyle modification can affect tumor microenvironment and ultimately, disease progression.
Background: Ovarian cancer (ovca) is the sixth most common malignancy in women; however, it is the deadliest gynecological malignancy in the United States. The literature over the past forty years has supported the concept of nulliparity and lack of oral contraceptive use as prime risk factors for the development of ovca. These factors are associated with increased numbers of ovulatory cycles, which play into the long-standing hypothesis of incessant ovulation as a potential cause of ovarian cancer. Infertility, which may be related to underlying ovulatory disorders as well as lower use of oral contraceptives and decreased parity, has also been proposed as a possible risk factor for ovarian cancer.

Although African American women (AAW) have a lower incidence of ovarian cancer compared to Caucasian women, they have an overall poorer 5-year survival rate (46 vs. 38%) respectively. The current literature has not studied the association between developing ovarian cancer in AAW with infertility.

Methods: We used data from 598 cases and 731 controls enrolled in the African American Cancer Epidemiology Study. Infertility was determined using section D of the AACES questionnaire and subjects were given the option of characterizing infertility as never/ever or greater than 12 months of unprotected intercourse without conception. Further classification in the infertility group was made to include women who were diagnosed with infertility by a doctor or other healthcare professional (DDI). Multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the association between infertility and ovarian cancer.

Results: Within our study population, any infertility (AI) was reported in 39% of cases and 30% of controls. DDI was reported by 16% of cases and 10% of controls. Cases had a higher prevalence of family history of breast or ovarian cancer, endometriosis, pelvic inflammatory disease, fibroids and ovarian cysts. The degree of association of these diseases was significantly higher in the DDI group. For AI, the OR was 1.45 (1.13-1.85) for developing ovarian cancer and the DDI group had a OR of 1.86 (1.24 – 2.81) when controlled for age, parity and oral contraceptive use. Prior to controlling for these factors, the odds ratio for developing ovca in the AI group was 1.56 (1.23 -1.97) and 1.96 (1.32-2.91) in DDI.

Conclusions: Factors associated with infertility (e.g. low parity, gynecologic diseases and smoking) were associated with ovarian cancer in this population. AI and DDI were both associated with ovarian cancer. Stronger associations were observed in the DDI group. Controlling for oral contraceptive use and parity attenuated the associations. Therefore, in a population of AAW, we observed a positive association between infertility and ovarian cancer. This association may be due, in part, to the decreased use of oral contraceptives and parity among those women.
Correlation of Functional Lung Heterogeneity and Dosimetry to Radiation Pneumonitis using Perfusion SPECT/CT and FDG PET/CT Imaging

Howard J. Lee Jr, Jing Zeng, Hubert Vesselle, Shilpen A. Patel, Ramesh Rengan, Stephen R. Bowen
RSNA Research Medical Student Grant

Background: Radiation induced pneumonitis is a clinically significant issue in patients undergoing definitive radiotherapy to the thorax, with incidence rates as high as 30%. The risk of pneumonitis is thought to be a major limiting factor to the dose that can be safely delivered to lung cancers that are at high risk for local failure. Interrogation of functional lung imaging modalities such as perfusion SPECT/CT scans and FDG PET scans can identify metrics that, in radiotherapy planning, allow selective avoidance of highly functioning lung regions with the overall goal of mitigating pulmonary toxicity.

Methods: Radiation treatment planning CT scans were co-registered with both pretreatment perfusion SPECT/CT scans and FDG PET/CT scans of 28 patients who underwent definitive thoracic radiation. Clinical radiation pneumonitis was defined as grade ≥ 2 (CTCAE v4). Anatomic lung dose-volume parameters were collected from the treatment planning scans. Functional dose-volume parameters were calculated from pre-treatment perfusion SPECT/CT and FDG PET/CT scans using a framework we have previously described. Baseline descriptors of both perfusion and FDG uptake heterogeneity throughout the lung were also calculated. Logistic regression characterized the predictive accuracy of features for incidence of grade ≥ 2 pneumonitis, while a Benjamini-Hochberg correction was applied to reduce the risk of false discoveries.

Results: Two anatomic lung dosimetric parameters, three perfusion dosimetric parameters, and one FDG PET dosimetric parameter were identified as candidate predictors of grade ≥ 2 radiation pneumonitis (AUC > 0.84, p < 0.05). Cutoff values with 100% sensitivity and > 65% specificity were calculated for each significant parameter. Cross-correlation analyses between parameters indicated that certain pairings with low correlation (Spearman ρ < 0.7) offer independent predictive information. Baseline measures of lung function heterogeneity were not significantly associated with pneumonitis incidence.

Conclusions: The application of our framework showed differences in anatomic and functional lung dosimetry between patients with and without pneumonitis in this patient cohort, with more perfusion metrics than SUV metrics showing correlation to pneumonitis outcome. Utilizing these functional lung parameters may help risk stratify patients for radiation pneumonitis before undergoing radiotherapy and inform plan modification. Further investigations and validation of the parameters we defined are ongoing in a related prospective study at our institution.
Cell Engineering of Induced Pluripotent Stem Cell-Derived Hemogenic Endothelium

Jerry C. Lee, Ryohichi Sugimura, George Q. Daley

HHMI Medical Research Fellowship, ASH HONORS Award, AMA Foundation Seed Grant

Background: Autologous cellular replacement for curative therapy of hematological malignancies and primary immunodeficiencies has been limited by the inability to yield functional hematopoietic stem cells (HSCs) from patient-derived induced pluripotent stem cells (iPS). Although previous approaches have produced immortalized cells with HSC-like morphology and cell surface markers, they have failed to demonstrate multi-lineage potential or secondary bone marrow engraftment in murine hosts – the gold standards for demonstrating HSC self-renewal and differentiation. Building upon recent evidence that HSCs derive from the definitive hemogenic endothelium (HE) of the embryonic mesoderm, we now set out to engineer iPS-derived HSCs by directed differentiation, and to investigate potential applications for modeling genetic blood diseases in vitro.

Methods: Following embryoid body formation, human iPS derived from bone marrow mesenchymal stem cells underwent stepwise, morphogen-directed differentiation into HE, followed by candidate screen of 26 HSC-specifying transcription factors (TFs) previously identified by HE and fetal-liver HSC expression profiling. TFs sufficient for murine engraftment were determined by genomic PCR. To model human disease, dermal fibroblast-derived iPS from a hypomorphic RAG2 Omenn syndrome patient were differentiated into HSCs, and cocultured with MS5 or OP9-DL1 stromal cells to induce B or T cell development. Fluorescence-activated cell sorting (FACS) was performed weekly for 6 weeks after initiating lymphoid differentiation.

Results: Five transcription factors (RUNXI, ERG, LCOR, HOXA5, HOXA9) were sufficient to engraft GLY-A+ erythrocytes, CD33+ myelocytes, CD15+ CD31+ neutrophils, CD19+ IgM+ B and CD3+ T cells in primary and secondary murine recipients for 12-14 weeks. Functional characterization of terminally differentiated engrafted cells included adult beta globin expression and enucleation for erythropoiesis, cytokine activation from myeloperoxidase exposure for myelopoiesis, and B/T cell surface markers by flow cytometry as well as PMA/Ionomycin stimulation for lymphopoiesis. From the mutant RAG2 iPS-derived HSCs, the cell population was characterized by the predominance of myeloid progenitors (CD38+CD45+CD45RA+) with roughly 5% of progenitors characterized as common lymphoid progenitors (CD10+CD34+CD45RA−), after 1 week of lymphoid-directed differentiation. Wildtype iPS-derived HSCs produced CD19+IgM− B cell progenitors as well as mature IgM+ B cells, which were comparable to cord blood controls; CD3+CD4+CD8+ T cells were also identified after 3 weeks. However, RAG2-mutant iPS were unable to generate CD19+ B cells and arrested at the CD5+CD4− early T cell stage.

Conclusions: This is first study to date that demonstrates engraftable and multi-lineage iPS-derived HSCs. Our approach of morphogen-driven differentiation and TF-mediated cell fate conversion holds significant promise for modeling hematopoietic-immunologic disease in humanized mice and as a “disease-on-a-dish,” and for developing therapeutic strategies for genetic blood and immune disorders.
CaV1.2 gain-of-function mutation causes aortic valve stenosis

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**Background:** Aortic stenosis (AS) is a life-threatening valvular pathology that affects 2% of individual’s ≥65. The cause of AS is multifactorial, but studies have shown the transformation of valve cells to a chondrogenic/osteogenic lineage. A 2015 GWAS and eQTL mapping identified CACNA1C SNPs associated with AS, correlating to increased CACNA1C expression and increased intracellular Ca\(^{2+}\) signaling. CACNA1C encodes for the alpha subunit of the voltage gated L-type calcium channel Ca\(v\)1.2, which has not previously been shown to be involved in the development of AS. Currently, there are no proven methods of medical management to delay or halt progression. It is essential to understand the molecular mechanisms of AS for translational applications, and the role of Ca\(v\)1.2 or increased Ca\(^{2+}\) influx may provide further insight.

**Methods:** A CACNA1C LacZ reporter line was used to demonstrate Ca\(v\)1.2 expression pattern in valves. Two additional mouse models were generated to study the effect of increased calcium influx on the phenotype. A G406R knockin mutation in CACNA1C, seen in the multi-organ disorder Timothy Syndrome (TS2), causes generalized decreased channel inactivation leading to increased Ca\(^{2+}\) influx. A second model was created to evaluate localized effect of increased Ca\(^{2+}\) influx, from a G406R mutant CACNA1C transgene specifically turned on in valve interstitial cells via a Cre recombinase driven by the transcription factor Scleraxis (Scx-Cre model). We analyzed the aortic valves by histology to assess for change in cell morphology and calcification.

**Results:** From the LacZ reporter line, we can conclude that CACNA1C is expressed in the aortic valve annulus and is overexpressed in the transgenic model. The knockin and transgenic models reveal markedly increased chondrocyte-like transformation of valve cells in the annulus, as compared to wild type controls. The transgenic model showed more severe cell morphology changes compared to the knockin.

**Conclusions:** We can conclude that increased Ca\(^{2+}\) influx causes the transformation of valve interstitial cells to a chondrogenic lineage and is tissue autonomous. The model can be used to elucidate downstream regulatory mechanisms involved with cell morphology changes, which can be studied as possible targets for clinical treatment.
Long-Term Changes in White Matter Microstructure During Recovery from mTBI in a Civilian Population

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Background: Diffusion tensor imaging (DTI) has proven to be a useful biomarker of traumatic axonal injury (TAI) in mild Traumatic Brain Injury (mTBI). Several studies have demonstrated a link between structural white matter pathology and functional outcomes in mTBI, but there is a dearth of prospective studies examining the evolution of mTBI longitudinally, especially in longer timespans up to 1 year post-injury. This study aims to remedy exactly that in the hopes of answering how the TAI thought to be responsible for the pathology of mTBI evolves over time, which white matter tracts are involved, and how that structural evolution correlates with patients’ evolving functional cognitive performance.

Methods: We analyzed 3T DTI scans and neuropsychiatric testing outcomes in 31 mTBI patients without previous history of neuropsychiatric disease or substance abuse longitudinally at 1 month, 6 months, and 1 year post-injury. We additionally performed a cross-sectional analysis under those same conditions as compared to 36 healthy controls. Tract-based spatial statistics (TBSS) were used to run voxel-wise nonparametric analysis of the DTI scans. Statistical comparisons of were performed using permutation testing, with corrections for multiple voxel-wise comparisons using threshold-free cluster enhancement (TFCE). Changes in fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were analyzed and correlated to changes in neuropsychiatric testing outcomes.

Results: Our results demonstrate an increase in FA from 1 month to 1 year post-injury, especially noticeable after 6 months, and a decrease in MD, AD, and RD from 1 month to 1 year post-injury. These changes in white matter microstructural anatomy, consistent with recovery, correlate with improvement in functional cognitive testing outcomes, especially as they relate to attention, executive function and planning, processing speed, and memory. The specific white matter tracts where structural recovery correlated with improved functional outcomes are the periventricular white matter tracts previously found to be disproportionately important to the structural connectome. When compared to healthy control subjects, mTBI patients demonstrated an increased FA and decreased MD, AD, and RD at 1 year post-injury – a supranormalization of chronic mTBI patients’ DTI parameters relative to healthy controls.

Conclusions: If we take higher FA to be indicative of greater white matter microstructural integrity, then we conclude that better structural outcomes in white matter integrity, especially in periventricular white matter tracts with disproportionately high importance to the structural connectome, correlate with better functional outcomes in attention, planning, calculation ability, auditory information processing speed/ability, and response inhibition in mTBI patients up to 1 year post-injury.
1. **Melissa Abel** – Host preparative lymphopenia increases the efficacy of CAR T cells for glioblastoma through depletion of regulatory T cells and increased access to homeostatic cytokines.

2. **Bradley Ackerson** – BRD4’s Localization and Role in the DNA Damage Response during Mitosis.


4. **Muhammad Hassan Alkazemi** – Radical and Partial Nephrectomy in Children and Young Adults: Equivalent Readmissions and Postoperative Complications.

5. **Muhammad Hassan Alkazemi** -- Spina Bifida Patients in the Emergency Room Setting: Are Presenting Diagnoses Associated with Inpatient Admissions?


8. **Olayode Babatunde** -- A Crowdsourced Approach to Genomic Annotation.


11. **Peter Bittar** -- Implementation of a Prospective, Standardized Data Collection System for the Comprehensive Appraisal of Cleft Care.

12. **David Carpenter**-- The incidence of carotid stenosis in head and neck cancer patients after radiation therapy.

13. **Doreen Chang**-- Perineal Approach to Rectal Prolapse Repair is Associated with Less Morbidity and Equivalent Durability at One Year Compared to Abdominal Repair.
14. **Jonathan Chang** -- Efavirenz use and risk of depression and suicidal ideation in HIV-infected adults receiving antiretroviral therapy in southwestern Uganda.

15. **Leslie Chang** -- Timing of Postdischarge Follow-Up and Medication Adherence among Heart Failure Patients.

16. **Curry Cheek** -- Best Strategies for Mobile Health Application Development and Diabetes Management.

17. **Sean T. Chen** -- Impact of Polyvascular Disease on Patients with Atrial Fibrillation: Insights from Rivaroxaban versus Warfarin in Non-valvular Atrial Fibrillation (ROCKET AF).

18. **Tracy Cheng** -- Timing and Frequency of Sinus Surgery are Associated with Lung Transplant Outcomes in Cystic Fibrosis Patients.


22. **Keithara Davis** -- *In vivo* measurement of time-dependent stress recovery in tibiofemoral cartilage after exercise-induced strain.

23. **Michael Dworkin** -- Use of continuous glucose monitors to normalize hemoglobin A1C for individual non-glycemic factors in adults with type 1 diabetes.

24. **Sara Encisco** -- Alpha-cell regulation of insulin secretion: diverse signals and mediators.

25. **Julia "Jamie" Farquhar** -- Patterns and Predictors of Pain following Lung Transplantation.

26. **Chelsea Feldman** -- Stromal Interaction Molecule 1 (STIM1) is required for normal uterine contraction and is altered in obesity.
27. Brock Gamez-- Wound Infiltration With an Elastomeric Pump for Analgesia After Cesarean Delivery: A Randomized Controlled Study.

28. Lauren Groskaufmanis-- Shared Medical Appointments for Prenatal Care: Maternal and Neonatal Health Outcomes.

29. Tracy Han-- No-Shows in Adult Urology Outpatient Clinics: Economic and Operational Implications.


31. Nathaniel Harris-- Patient-Reported Disease Activity and Adverse Pregnancy Outcomes in Systemic Lupus Erythematosus and Rheumatoid Arthritis.

32. Daniel Harrison-- ALS Reversals: Demographics, Disease Characteristics, Treatments, and Co-morbidities.

33. Sehj Kashyap-- Evaluation of a training program for Indian frontline healthcare providers to improve their supports for patient activation.

34. Neha Kayastha-- Open Notes: A Qualitative Study of Oncology Patients’ Experiences Reading their Cancer Care Notes.


38. Christopher Kline-- Using a Novel Proteomics Approach to Identify mGluR5 Regulatory Proteins \textit{In Vivo}.

39. Allison Kratka-- Finding healthcare prices online: how hard is it to be an informed healthcare consumer?

40. Harold Leraas-- Postoperative Venous Thromboembolism in Children is Increased in Setting of Cancer or Infection.
41. **Jonathan Li**-- Quantitative DTI Metrics in a Canine Model of Krabbe Disease: Comparisons vs. Age-Matched Controls across Multiple Ages.

42. **Jesse Liu**-- Evaluation of colorimetry and biomechanical properties in wounds of dermatologic patients with postoperative infection.

43. **Colin Martz**-- Hypoxia inducible factor 1 alpha orchestrates resistance to the novel MAPK/ERK inhibitor SCH772984 by upregulating ABCG2 in a cyclin-dependent kinase 8/19-dependent fashion.

44. **Emily Mattoon**-- Project CALM: Confusion Avoidance Led by Music, A Quality Improvement Initiative to Reduce Postoperative Delirium.

45. **Dana Middleton**-- DTI Tensor Shape Analysis for Assessment of Regional White Matter Differences.

46. **Jessica Narloch**-- Patients with Breast Cancer Brain Metastases Demonstrate an Improved Overall Survival over the Past Two Decades.

47. **Neel Nath**-- Utility of Staging PET-CT in Patients with Melanoma and a Positive Sentinel Lymph Node Biopsy.

48. **Stephanie Pagliuca**-- Quality of Hospital Management is Associated with Neonatal Outcomes in India.

49. **Sherveen Parivash**-- Alterations in hippocampal subfield volume in collegiate athletes participating in high-contact sports: A 5-year longitudinal study.

50. **James Parra**-- Neuropeptides and Scleroderma.

51. **Michael Peterson**-- A Retrospective Descriptive Study of Patients Treated in the Durham Veterans Affairs Leg Ulcer Clinic, an Equal Access Setting.

52. **Cary Politzer**-- Trends in Opioid Utilization before and after Total Knee Arthroplasty.

53. **Charles Puza**-- Investigation of mechanisms of thermal ablation zone enlargement when combined with transarterial embolization for treatment of liver tumors.

54. **Krystina Quow**-- Enhancing Employee Empowerment by Celebrating the Red Dots.
55. **Faith Rialem**--Knowledge and Perceptions Regarding Palliative Care among Religious Leaders in Uasin Gishu County: Survey and Focus Group Analysis.

56. **Alvin Justin Rucker**--Understanding the contribution of CX3CR1+ myeloid cell-specific TNF- in mediating hypertensive end organ damage.

57. **Monisha Sachdev**--Effects of Dextromethorphan in a SUDEP mouse model.

58. **Priscille Schettini**--Keeping Care Connected: E-Consultation Program Improves Access to Nephrology Care.

59. **Emily Schwitzer**--Prevalence and Clinical Importance of Sarcopenia in Women with Breast Cancer Treated with Antiandrogen Therapy.

60. **Gillian Smelick**--An Evaluation Of The Effectiveness of the HPV Vaccine In Preventing Genital Warts and Cervical Disease Among Young Women at Duke.


64. **Bo Sun**--Dengue virus activates cGAS through the release of mitochondrial DNA (mtDNA).


66. **Michelle Tang**--Genital Mycoplasmas and Vaginal Fluid Antimicrobial Peptides in Pregnancy.

67. **David Tat**--Milk and other dairy foods in relation to prostate cancer recurrence: data from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE™).

68. **Westin Tom**--Effect of Increased Fluid Intake on 24-hour Urinary pH in Stone Formers with Low Urine Volume.
69. Christopher Toote--The B cell repertoire and antibody maturation elicited by adjuvanted HIV envelope vaccines in infants.

70. Matthew Wagner--Protocolized Hemostatic Factor Use in Major Thoracic Aortic Surgery.


72. Erin Wolf--Female Sex Diminishes Hypertensive Response of Vascular Type 1A Angiotensin Receptors.

73. Cole Ziegler--Unexpected Cardiac MRI Findings in Patients Presenting to the Emergency Department for Potential Acute Coronary Syndrome.

Host preparative lymphopenia increases the efficacy of CAR T cells for glioblastoma through depletion of regulatory T cells and increased access to homeostatic cytokines

Melissa L. Abel, CM. Suryadevara, Pakawat Chongsathidikiet, Steven Shen, Luis Sanchez-Perez, John H. Sampson
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Background: Glioblastoma (GBM) is the most common primary malignant brain tumor and is uniformly lethal. The adoptive transfer of T-cells genetically engineered to express chimeric antigen receptors (CARs) represents a promising strategy to safely eradicate tumor cells in the brain. CARs are recombinant transmembrane proteins that couple the antigen-binding regions of an antibody with the signaling components of T-cell receptors. We developed CARs that recognize the tumor-specific mutation, EGFRvIII, which is commonly expressed GBMs. We investigated the therapeutic efficacy of CARs delivered intracranially in mice bearing established GBM. Although CARs were capable of prolonging survival, efficacy was limited by poor CAR survival and exhaustion. We hypothesized that hosts would benefit from total body irradiation (TBI) lymphodepletive preconditioning, based on the rationale that this would both 1) reduce the competition for CARs for homeostatic cytokines (e.g. IL-7/IL-15) and 2) deplete immunosuppressive regulatory T cells (Treg).

Methods: Experiments required C57BL/6 mice, and IL-7−/−/IL-15−/− and DEREG transgenic mice that allow for depletion of FoxP3+ Tregs. We utilized the CT2A-EGFRvIII GBM cell line. 5x10⁴ tumor cells were implanted in the brain. 7 days later, mice were treated with either vehicle, +/- 5Gy TBI, and +/- 2x10⁵CARs. CARs infused at the coordinates of tumor implantation. Survival was followed. In experiments requiring temozolomide (TMZ), 400 mg/kg was administered as a single dose intraperitoneally 24 hours prior to CAR infusion.

Results: Host lymphodepletion with 5Gy TBI prior CAR therapy resulted in 90-100% long-term cures. Our analyses revealed that CARs infused in this context were long-lived and showed fewer markers of T-cell exhaustion. We then evaluated whether selective depletion of Tregs would enhance CAR therapy in non-lymphodepleted hosts. Treg depletion led to a partial improvement in overall survival. Therefore, we sought to evaluate the contribution of the homeostatic gamma chain cytokines, IL-7 and IL-15, which are available for CAR consumption in mice that are lymphodepleted. To do this, we performed lymphodepletion in mice genetically deficient in IL-7 and IL-15, and found that CAR efficacy was dramatically reduced in this context. To evaluate the clinical translatable of our observations, we used TMZ chemotherapy for preconditioning (in lieu of 5Gy TBI) prior to CARs, and found that TMZ enhanced CAR therapy and dramatically improved survival outcomes.

Conclusions: Our findings support the hypothesis that CAR efficacy can be limited by host immunosuppression and poor access to IL-7 and IL-15 cytokines within the brain. Most importantly, we demonstrate that hosts can be sufficiently preconditioned to enhance CAR immunotherapy using clinically relevant doses of TMZ chemotherapy, which is the standard of care for patients with GBM. These results are highly consequential, as this work has resulted in a clinically feasible and translatable strategy to advance CAR immunotherapy for patients with GBM, where the need for novel therapies is dire.
BRD4’s Localization and Role in the DNA Damage Response During Mitosis

Bradley G. Ackerson, Lei Zhao, Drake S. Edwards, Scott R. Floyd

**Background:** Following DNA damage, signaling networks block progression through the cell-cycle and initiate DNA repair to continue cell growth, or stop cell growth by triggering cell death or senescence. These cell signaling consequences following DNA damage are important for cancer cell responses to radiation therapy. Via a screen for modifiers of the signaling response to ionizing radiation, we previously identified an isoform of the BET-bromodomain protein family member BRD4 as an inhibitor of the DNA damage signaling response. We find that this isoform is tightly associated with chromatin and results in a more compact chromatin structure and increased radiation-induced lethality when over-expressed. BET-bromodomain proteins interact with acetylated lysine via tandem N-terminal bromodomains, and several studies have implicated BRD4 in the regulation of transcription. In addition, prior studies have demonstrated a role for some BRD4 isoforms in mitosis, and indicate that BRD4 might act as a mitotic “bookmark” to preserve histone acetyl marks through cell division. We hypothesized that BRD4 relocates to the chromatin during mitosis, and that this relocalization is integrally involved in the cell’s passage through mitosis and response to DNA damage.

**Methods:** The Fluorescent Ubiquitination Cell Cycle Indicator (FUCCI) system was utilized to easily identify and isolate cells in certain phases of mitosis (S, G2 or M). Using both transient transfection and immunofluorescence, BRD4’s mitotic localization was visualized. Cells were imaged for >24 hours with four-minute resolution using the Olympus VivaView live-cell microscope to understand how this localization changes, and specifically how cells undergoing mitosis are affected by various DNA-damaging conditions. We used JQ1 (a small molecule inhibitor of BRD4’s ability to associate with the chromatin) to disrupt BRD4 during mitosis, and measured how this affects mitotic dynamics with and without 4 Gray ionizing radiation.

**Results:** We find that JQ1 interrupts the cell’s ability to successfully complete anaphase, specifically by inhibiting its successful completion of cytokinesis. When cells were imaged without JQ1, 0/17 mitotic events failed to complete cytokinesis. After the introduction of 250nM JQ1, 4/9 mitotic events were unable to complete successfully due to failure of cytokinesis, with another mitotic event resulting in mitotic catastrophe. Moreover, overexpression of BRD4 isoforms contributes to mitotic catastrophe.

**Conclusions:** These findings point to a critical role for BRD4 in mitotic chromatin dynamics and the cell’s ability to successfully complete anaphase. This implicates BRD4 as a potential target to modulate the cellular response to ionizing radiation.
Emergency department utilization by children of women receiving group prenatal care: a retrospective cohort study

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Background: The objective of this study is to investigate emergency department usage of infants born to mothers using different kinds of prenatal care: mothers using the CenteringPregnancy model of group prenatal care at the Durham County Health Department (DCHD) versus mothers using traditional prenatal care at the DCHD.

Methods: This study used a retrospective cohort design. The cohort was composed of mothers who received prenatal care at the DCHD and delivered at Duke Hospitals over one year. Data was collected from prenatal, labor and delivery, and postpartum medical records.

Results: Of the children born to the 5,579 women who delivered during the time interval selected, 691 children met eligibility criteria and had emergency department visit data available: 134 were enrolled in group care group and 417 were enrolled in traditional prenatal care group. There were no significant differences in proportion of patients using ED services between the two groups (16.2% group care v. 17.2% standard care, p=0.88).

Conclusions: There was no significant difference between the proportions of patients utilizing the emergency department in the first two months of life. There was no significant difference between proportion of patients utilizing the NICU or breastfeeding at hospital discharge or at 6 months of life.
Spina Bifida Patients in the Emergency Room Setting: Are Presenting Diagnoses Associated with Inpatient Admissions?

Muhammad H. Alkazemi, MS, Kristen Sanchez, MS, Ruiyang Jiang, MD, Steven Wolf, MS, Gina-Maria Pomann, PhD, and Jonathan C. Routh, MD, MPH

Background: Patients with spina bifida (SB) often experience comorbid conditions that lead to increased healthcare costs and rate of emergency department utilization and hospitalization than patients without the condition. Oftentimes, these comorbid conditions are potentially preventable. We aimed to provide a descriptive analysis of inpatient hospital utilization by patients with SB based on initial presenting diagnoses to the emergency department using state databases. Furthermore, we aimed to describe the relationship between these patients’ presenting diagnoses and their subsequent discharge or inpatient admission.

Methods: We analyzed the 2007-2010 State Inpatient Database (SID) and State Emergency Department Database (SEDD) for the states of CA, FL, UT, NY, and NC. We included patients diagnosed with SB based on ICD-9 codes (756.17, 741.0, 741.9, 741.00-03, and 741.90-93). In addition, only patients admitted to inpatient units from the emergency room were included. Patients with bladder extrophy, sacral agenesis, and lumbar spine agenesis were excluded. We described this population and constructed heatmaps to examine correlations between CCS codes for both inpatient admissions and ER discharges.

Results: We identified a total of 10,714 unique ER visits. 259 patients had at least one inpatient admission and 10,655 patients had at least one ER discharge. The average age was 26.7 years (SE 16.0). There were more female visits than male visits (58% vs. 41.7%). Medicaid was the most common primary insurer compared to Medicare and Private insurance (42.3% vs. 19% vs. 25.9%, respectively). Post-operative complications were identified in only 19.5% of the visits. The average number of diagnoses present for each admitted patient visit was higher than those discharged from the ED, 9.2 diagnoses (SE 5.2) vs. 4.5 diagnoses (SE 2.2). We observed that nervous system disorders (32%), UTI (30%), and headache (14%) were three of the most common diagnoses in patients admitted to inpatient unit. We did not find any strong correlations between CCS codes.

Conclusions: Patients with SB are different from the general population in terms of presenting diagnoses and demographic characteristics. The average number of diagnoses for admitted patients was higher than for those discharged. We did not find evidence to suggest CCS codes were correlated across inpatient admissions or patients who were discharged from the ER.
Radical and Partial Nephrectomy in Children and Young Adults: Equivalent Readmissions and Postoperative Complications

Muhammad H. Alkazemi, MS, Ruiyang Jiang, MD, Steven Wolf, MS, Gina-Maria Pomann, PhD, Elisabeth T. Tracy, MD, Henry E. Rice, MD, Jonathan C. Routh, MD, MPH

Background: Although the use of radical nephrectomy (RN) is the standard of care for most pediatric renal masses, there has been increasing interest in partial nephrectomy (PN) as an alternative. PN’s use remains controversial and there is scarce national-level evidence to compare outcomes with RN. This study aims to characterize the quality measures of readmission rates and postoperative complications using a nationally representative database.

Methods: The 2013 Nationwide Readmissions Database (NRD) was used to obtain RN and PN select postoperative data. ICD-9-CM codes were used to identify children (<10 y), adolescents (10-19 y) and young adults (20-30 y) diagnosed with benign and malignant renal tumors who were treated with an RN or PN. The presence of a 30-day readmission and the occurrence of postoperative complications were studied. A weighted multivariate logistic regression model was used to adjust for gender, insurance type, income, hospital type, and comorbidity.

Results: There were 962 patients (638 RN, 324 PN) that met inclusion criteria: 47% were children, 11% were adolescents, and 42% were young adults. Children and adolescents had the highest rates of RN whereas young adults had the highest rates of PN (p<0.0001). Overall, there was no significant association between the type of nephrectomy performed and the presence of a 30-day readmission or postoperative complication. Postoperative complication rates did not differ between RN and PN in all age groups.

Conclusions: There was no evidence of a difference between RN and PN in terms of postoperative readmissions or in-hospital complications.
Pediatric Traumatic Brain Injury Clinical Practice Guidelines: Systematic Review and Quality Appraisal

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Background: Traumatic brain injuries (TBI) are a significant cause of mortality and morbidity for children globally. Adherence to evidence-based treatment guidelines have been shown to improve TBI outcomes. To inform the creation of a pediatric TBI management guideline for a low and middle income country context, we assessed the quality of available clinical practice guidelines (CPGs) for the acute management pediatric TBI.

Methods: Articles were identified and retrieved from MEDLINE, EMBASE, Cochrane Library, LILACS, Africa-Wide Information and Global Index Medicus. These articles were screened by four reviewers independently. Based on the eligibility criteria, with the exception of literature reviews, opinion papers and editor’s letters, articles published from 1995 to November 11, 2016 which covered clinical recommendations, clinical practice or treatment guidelines for the acute management of pediatric TBI (within 24 hours) were included for review. A reference and citation analysis was performed. Seven independent reviewers from low, middle and high income clinical settings with knowledge of pediatric TBI management appraised the guidelines using the AGREE II instrument. Scores for the CPGs were aggregated by domain and overall assessment was determined.

Results: We screened 2373 articles of which 17 were retained for data extraction and guideline appraisal after reference and citation analysis. Except for one CPG from a middle income country, the majority (15/16) of the guidelines were developed in high income countries. Seven guidelines were developed specifically for the pediatric population, while the remaining CPGs addressed the acute management of TBI in both adult and pediatric populations. The Scandinavian Neurotrauma Committee (SNC, 2016) received the highest overall assessment score of 45/49 (91.84%) followed by the Scottish Intercollegiate Guideline Network (SIGN, 2009) and Brain Trauma Foundation (BTF 2012) both with scores of 44/49 (89.80%). CPGs from Cincinnati Children’s Hospital (CCH 2006) and Sao Paulo Medical School Hospital/Brazilian Society of Neurosurgery (USP/BSN, 2001) received the lowest score of 27/49 (55.10%) subsequently followed by the Appropriateness Criteria (ACR, 2015) with 29/49 (59.18%). The domains for scope and purpose and clarity of presentation received the highest scores across the CPGs, while applicability and editorial independence domains had the lowest scores with a wider variability in score range for rigor of development and stakeholder involvement.

Conclusions: To our knowledge, this is the first systematic review and guideline appraisal for pediatric CPGs concerning the acute management of TBI. Targeted guideline creation specific to the pediatric population has the potential to improve the quality of acute TBI CPGs. Furthermore, it is crucial to address the applicability of a guideline to translate the CPG from a published manuscript into clinically relevant local practice tools and for resource limited practice settings.
Prevalence and Cost Analysis of Chronic Pain after Hernia Repair: A Role for Neurostimulation

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Background: Chronic post-hernia repair pain affects an estimated 11-54% of patients following hernia repair. Chronic neuropathic post-hernia repair pain, specifically, has proven difficult to treat. The aim of this study was thus to assess the healthcare resource utilization (HCRU) and costs associated with chronic neuropathic post-hernia repair pain.

Methods: A retrospective longitudinal study was performed using the Truven MarketScan® database to identify patients who develop chronic neuropathic post-hernia repair pain from 2001 to 2012. Patients were grouped into Chronic Pain (CP) and No Chronic Pain (No CP) cohorts. Total, outpatient, and pain prescription costs were collected in the period of 5 years pre- to 9 years post-hernia repair. A longitudinal multivariate analysis was used to model the effects of chronic neuropathic post-hernia repair pain on total inpatient/outpatient and pain prescription costs.

Results: We identified 76,173 patients who underwent hernia repair and met inclusion criteria [CP: n=14,919, No CP: n=61,254]. Baseline characteristics were similar between the cohorts, with the CP cohort being younger and having a larger proportion of females. There was a trend for increased total inpatient/outpatient, outpatient, and pain prescription costs 1 year prior to hernia repair, when compared to 2 and 3-year baseline costs for both cohorts. In both cohorts, total inpatient/outpatient and outpatient costs remained elevated from baseline at 9 years post-repair; pain prescription costs returned to baseline for both cohorts. In the longitudinal analysis, the chronic pain diagnosis year (excluding index hernia repair) was associated with a 1.75-fold increase (p<0.001) in total inpatient/outpatient costs and a 2.26-fold increase (p<0.001) in pain prescription costs versus all other years. In the same analysis, the CP cohort had a 1.14-fold increase (p<0.001) in total inpatient/outpatient costs and a 2.00-fold increase (p<0.001) in pain prescription costs.

Conclusions: Our study demonstrates a significant increase in HCRU and costs associated with chronic neuropathic post-hernia repair pain. While the current treatment paradigms are effective for most patients, select refractory populations may benefit from neurostimulation. Further studies are necessary to understand the impact neurostimulation and DRG stimulation may play in mitigating both costs and interference to quality of life caused by chronic neuropathic post-hernia repair pain.
A Crowdsourced Approach to Genomic Annotation

Olayode Babatunde, Othmane Jadi, Qiu Qin, Razvan Panea, Sandeep Dave

**Background:** Advancements in sequencing technology has greatly increased the pace of genomic research. However, the data thus generated are dispersed across many databases. Furthermore, the depth of genomic information has made it rather burdensome to analyze the growing genomic data in a useful way. We developed the CrowdSeq Human Exome Database (http://crowdseq.davelab.org) as a comprehensive and freely assessable web resource for investigating, visualizing, and exploring genomic data. Here, we provide a practical guide to the structure and visualization features of the CrowdSeq Database and provide an explorative analysis of the BRAF gene and its V600E variant to highlight features of the website.

**Methods:** CrowdSeq combines relevant genomic information on all possible single nucleotide variant (SNVs) in the human exome, and provides an interface for all users to annotate any variant. The database reduces molecular profiling data curated from a diverse set of databases and studies into readily comprehensible information that provides insight into how genes and variants relate to cancers and other determinants of health. Distributed Resources are extracted using scripts written in python 3.0 and stored in a SQL relational database. Gene and Variant Frequencies are plotted on the fly on the CrowdSeq website for each gene or variant using a JavaScript API of Plotly. The back-end of the CrowdSeq web user interface was developed using the Python web framework Django.

**Results:** The database provides functional annotations for all the gene coding regions and for all possible synonymous and nonsynonymous SNVs in the human exome (approximately 19 thousand genes and 97 million variants respectively). CrowdSeq provides graphical summaries of gene and variant level data from multiple studies, scores and metric access, cancer frequency analytics, and direct links to other databases for more information. Critically, the web-interface enables the input of user-supplied annotations, allowing individuals to supplement the automated mined data and share with other users. Analysis of BRAF gene indicated that the majority of mutations in the BRAF gene are missense across different cancers. Deleterious variants, as scored by CADD, are highly clustered around the tyrosine kinase domain. This abnormality is visually displayed in an easily comprehensible lollipop plot format. In particular, the BRAF V600E mutation was found in a large proportion of thyroid cancer, melanoma, and colorectal adenocarcinoma (.57, .42, .14 respectively).

**Conclusions:** Our methodology represents a novel and clinically relevant way to visually display gene and variant alteration across the genome. Our results indicate the gene and variant frequencies are in line with other established analytic databases including cbiportal. The simplistic user interface and query structure allows users, regardless of expertise, to explore and analyze gene and variant level data. Since all possible synonymous and non-synonymous variants are accounted for, the database provides an initial base of information for new variant discoveries.
Rapamycin Directly Alters Human Endothelial Cell Alloimmunogenicity

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Background: The mTOR inhibitor rapamycin (Rapa) is known to suppress T cell function. However, many of its in vivo effects, particularly its synergistic effects with costimulation blockade, cannot be explained through its known effects on T cell activation. Vascular endothelial cells (ECs) are the first barrier between host immunity and the allograft and thus play a central role in allo-recognition and costimulation. We hypothesized that Rapa may directly alter ECs and render some of its effects through alteration of EC alloimmunogenicity rather than T cell immunosuppression.

Methods: Human ECs were stimulated by TNF-α or IFN-γ for 72 hours with or without rapamycin or vehicle solution (VS). The expression of HLA-class I and II, adhesion molecules, costimulatory molecules, and inhibitory molecules PD-L1 and PD-L2 were assessed using flow cytometry. Peripheral blood mononuclear cells labeled with VPD-450 were stimulated by resting, rapamycin-conditioned, and VS-conditioned ECs and the allo-specific T cell responses were assessed by flow cytometry to detect cell proliferation.

Results: Resting, as well as cytokine stimulated ECs had altered expression of adhesion, costimulatory, and inhibitory molecules in the presence of rapamycin. Resting endothelial cells displayed a significant increase in OX40L (p=0.0017), CD54 (p=0.024), CD58 (p=0.0067), as well as a significant decrease in CD40 (p<0.0001) expression. Rapamycin/TNF-α treated ECs demonstrated higher expression of HLA-ABC (p=0.0083), CD40 (p=0.035), OX40L (p=0.0049), CD54 (p=0.027), CD58 (p=0.017). Rapamycin/IFN-γ treated ECs showed significant increase in CD54 expression when compared with VS/IFN-γ treated-ECs (p=0.019). There was significantly higher PD-L1 (p<0.001) and PD-L2 (p<0.001) expression on rapamycin-treated ECs compared to untreated ECs. ECs treated with rapamycin/IFN-γ showed higher PD-L1 (p=0.021) and PD-L2 (p=0.0141) expression when compared to VS/IFN-γ treated-ECs. Furthermore, rapamycin/TNF-α conditioned ECs significantly upregulated PD-L1 (p=0.0061) and PD-L2 (p=0.0012) when compared to VS/TNF-α treated ECs. Rapamycin-treated ECs significantly inhibited allo-specific CD4+ (81.32±9.36%, p=0.001) and CD8+ (60.56±13.8%, p=0.007) cell proliferation when compared with VS treated ECs. Importantly, ECs induced allo-specific T cell proliferation with significantly higher levels of PD1 expression on proliferating CD4+ (72±6.2%, p=0.001) and CD8+ cells (53.75±6.35%, p=0.0069) than non-proliferating cells.

Conclusions: Rapamycin alters the surface phenotype of ECs such that they show enhanced expression of the inhibitory signals PD-L1 and PD-L2. Allo-specific proliferating T cells upregulate PD1 expression, and rapamycin treated ECs exhibit inhibitory effects in reducing allo-specific T cell proliferation, when compared with non-rapamycin treated ECs. This finding implies a direct role of rapamycin in altering donor EC alloimmunogenicity, leading to inhibition of the alloimmune response. Furthermore, we are currently examining the effects of blocking the PD ligand/PD1 pathway.
Exploring Head and Neck Cancer Survivorship Needs and Interventions

Callie Berkowitz, Mentors: Bridget Koontz, Sophia Smith
Duke Institute for Health Innovation Scholarship

**Background:** Head and neck cancer (HNC) survivors experience significant sequelae of treatment, including difficulties with eating/drinking, communication, and pain. Careful oncology and primary care follow-up is necessary for surveillance of recurrence/secondary cancers. Survivorship care plans (SCPs), which are individualized treatment summaries, have been advocated to improve after-treatment care, but evidence is limited. Mobile health (mHealth) technology has the potential to improve implementation and engagement with survivor care. We aim to better understand the needs, knowledge, and preferences of HNC patients and PCPs via internally developed surveys, and study the role of mHealth.

**Methods:**

**HNC Patient and PCP Needs:** Using convenience sampling, we surveyed 41 HNC patients within 3 months of finishing treatment using a paper-based survey as they presented to oncology clinic between July-November 2016. In January 2017, we deployed a Qualtrics-based electronic survey to 240 PCPs via departmental email (N=28, RR=12%). Descriptive statistics were used to characterize responses. **Survivorship Care Plans:** We are surveying 3 cohorts of HNC patients at early follow-up appointments: 1) patients who did not receive a SCP 2) patients who received SCP based a standardized template and 3) patients who received an enhanced SCP. We are comparing survivorship knowledge, PTSD symptoms, quality of life, and distress between cohorts. **Mobile Tools for Cancer Care:** After developing a structured interview guide focusing on mHealth implementation, we interviewed 15 oncology providers about attitudes and preferences. De-identified audio recordings were transcribed and coded for emerging themes.

**Results:**

**HNC Patient and PCP Needs:** 44% of patients lacked regular dental care and 15% lacked PCPs. HNC survivors’ correct responses to side-effect knowledge questions were lowest for items regarding hearing loss (15%), sleep (33%), tiredness (38%), and anxiety (49%). Nearly one-third of PCPs (29%) found it difficult to coordinate care with oncology providers. Few PCPs felt confident screening for HNC recurrence (29%) and managing late/long-term side effects of therapy (32%). **Survivorship Care Plans:** This study is ongoing; we have enrolled 1 patient in cohort 1 and 4 patients in cohort 2. Global QoL scores on the EORTC QLQ-C30 ranged from 67-92 on a 100-point scale. Correct response rate on the knowledge survey ranged from 73%-85%. Most patients (80%) were interested in using mobile apps related to cancer care. **Mobile Tools for Cancer Care:** Participants included physicians (n=8), advanced practice (n=3) and supportive services (n=4) providers. Oncology providers reported limited exposure to mHealth apps in patient care, but were generally open to “prescribing” apps in the future. Key themes included opportunities of mobile app use (health promotion, tracking symptoms, and engaging patients) and barriers to implementation (access to technology, responsibility, workflow and the source of the app itself).

**Conclusions:** We study found significant gaps in HNC knowledge and care among survivors and PCPs. Our ongoing study will help clarify the role of SCPs. Mobile survivorship tools should be explored given patient interest and oncology provider openness.
Implementation of a Prospective, Standardized Data Collection System for the Comprehensive Appraisal of Cleft Care

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**Background:** Long-term outcomes research for cleft lip and/or palate (CL/P) has been very challenging, in part due to lack of standardized outcome measures. In 2016, a “standard set” of outcome measures for the comprehensive appraisal of cleft care was proposed by the International Consortium for Health Outcomes Measurement (ICHOM). The standard set defines specific outcome measures in multiple domains of care for children with CL/P; however, prior to implementation, this conceptual framework must be translated into a practical framework customized for the specific constraints that exist in each center. Herein, we describe this process for one cleft team.

**Methods:** Implementation was accomplished in several stages. An initial one-month stage for creating patient- and clinician-reported forms and protocols for gathering data. In the next months, team members were trained and the system was tested thoroughly; finally, the system was deployed in live practice in clinic. Success of the implementation was appraised using the RE-AIM framework to assess reach, effectiveness, adoption, implementation, and maintenance.

**Results:** 98% of eligible patients agreed to participate in the study. All team members participated. Of the required data points prescribed by the standard set, 94% were successfully captured. Friction points were identified and adaptations were made to address them. Specifically, to clarify which patients needed data collection, paper reminders were affixed to charts; primary clinicians were required to assume data-entry responsibility to avoid missed data when rotating residents left team; clinicians were required to submit data by end of clinic day and email reminders were used to further improve effectiveness. Development cost for the system was $7707. Average additional time for clinicians to use the system was 21 min/week.

**Conclusions:** All conceptual frameworks for outcomes studies must first be tailored to suit the environment; otherwise, they cannot be practically implemented and sustained. In this paper, we present how this process was accomplished for a multidisciplinary cleft lip/palate team using the ICHOM standard set. The general principles outlined may help other teams in implementing the standard set or other conceptual frameworks within their own hospitals.
The incidence of carotid stenosis in head and neck cancer patients after radiation therapy

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Background: Head and neck radiation therapy (RT) is a known risk factor for cerebrovascular disease, however the carotid artery dose associated with increased risk has not been established. We evaluated the incidence of carotid artery stenosis (CAS) in head and neck cancer (HNC) patients treated with RT and assessed whether a dose-response effect exists between carotid artery dose and CAS.

Methods: We retrospectively reviewed records of HNC patients undergoing carotid ultrasound screening after curative-intent RT between January 2000 and May 2016. CAS was defined as ≥50% stenosis on imaging or cerebrovascular disease (stroke or transient ischemic attack [TIA]). Actuarial CAS rates were calculated by Kaplan-Meier method. Univariate Cox proportional hazards regression analyses were utilized to predict time to CAS development based on carotid dosimetric parameters and clinical factors. Multivariate Cox proportional hazards models including neck dissection, number of Framingham risk factors, and each carotid artery or bulb dose parameter (Dmax, Dmean, V50, V70) predicted CAS risk.

Results: 366 patients met inclusion criteria. Median time from RT completion to last follow-up was 4.1 yr (IQR 2.3–6.8). Actuarial risks for cerebrovascular disease (asymptomatic CAS, stroke, or TIA) were 19.7% (95% CI 15.3–25.2%) and 35.1% (95% CI 27.0–44.7%) at 5 and 9 years, respectively. Univariate analysis showed that smoking (HR 1.7; 95% CI 1.1–2.7, p=0.02), HLD (HR 1.6; 1.03–2.6, p=0.04), DM (HR 2.8; 1.6–4.8, p<0.001), CAD (HR 2.4; 1.4–4.2, p=0.002), PAD (HR 3.6; 1.1–11.6, p=0.03), and Framingham risk factors (HR 1.3 per factor; 1.1–1.5, p=0.001) were significantly associated with increased CAS. In multivariate models, carotid artery/bulb Dmax, Dmean, V50 and V70 values were not predictive of time to CAS.

Conclusions: CAS incidence is high after head and neck radiotherapy, gradually rising over time. No clear dose-response effect between carotid dose and CAS was identified. Carotid artery screening and preventative strategies should be employed in this high-risk patient population.
Perineal Approach to Rectal Prolapse Repair is Associated with Less Morbidity and Equivalent Durability at One Year Compared to Abdominal Repair

Doreen Chang, Megan C. Turner, Zhifei Sun, Brian F. Gilmore, Cecilia T. Ong, Christopher R. Mantyh, John Migaly, Harvey G. Moore

Background: There is a perceived durability advantage for abdominal approaches for rectal prolapse repair compared with perineal approaches. However, this has not been validated using a large contemporary dataset. We aim to compare the durability and time to re-intervention between abdominal and perineal approaches for rectal prolapse.

Methods: This was a retrospective review of a multistate database of patients undergoing rectal prolapse repair. The 2007-2010 Healthcare Cost and Utilization Project (HCUP) State Inpatient Database was reviewed to identify patients with rectal prolapse who underwent abdominal or perineal approaches for surgical management. After multivariable adjustment for demographic and clinical variables, rate and timing of re-intervention for prolapse was compared between groups.

Results: Among 4,504 patients who underwent rectal prolapse repair, 2,334 (51.8%) were abdominal and 2,170 (48.2%) perineal. Postoperative complication rates were equivalent for surgical site infection, abscess formation, sepsis, pneumonia, venous thromboembolism, renal failure, and postoperative bleeding. However, the abdominal approach had higher rates of postoperative anastomotic leak, respiratory failure, and a longer length of stay. The rates of re-intervention were equivalent between the two approaches at one year. Patients who required re-intervention in the first year had similar time to reoperation (28.8 weeks for abdominal vs. 29.3 for perineal (p=0.66).

Conclusions: Perineal approach for rectal prolapse results in decreased postoperative complications, shorter length of stay, and equivalent durability at one year and equal time to re-intervention compared to the abdominal approach. We conclude that the perineal approach should be considered for an expanded range of patients with rectal prolapse.
Efavirenz use and risk of depression and suicidal ideation in HIV-infected adults receiving antiretroviral therapy in southwestern Uganda

Jonathan L. Chang, Alexander Tsai, Jessica Haberer, Yap Boum, Jeffrey Martin, Peter Hunt, David Bangsberg, Mark J. Siedner
Harvard Doris Duke International Clinical Research Fellowship

Background: There is conflicting evidence on the morbid neuropsychiatric effects of efavirenz and limited data in sub-Saharan Africa, where efavirenz remains commonly used.

Methods: We analyzed data from 704 participants in the Uganda AIDS Rural Treatment Outcomes Study, a cohort of adults in southwestern Uganda observed every 3-4 months from 2005-2015. The primary exposure was efavirenz use, defined as a prescription including efavirenz for seven consecutive days and >60/90 days prior to a visit. Outcomes of interest were: 1) depression, defined by a mean score >1.75 on the Hopkins Symptom Checklist; and 2) self-reported suicidal ideations (SI). We fitted generalized estimating equations (GEE) logistic regression, Cox proportional hazards, and time-dependent inverse probability-weighted marginal structural models to examine the association between efavirenz and risk of depression and SI, accounting for baseline depression and SI, demographics, CD4 count, viral suppression, ART duration, year of ART initiation, quality of life, and heavy alcohol use.

Results: There were no differences at ART initiation in depression or SI among those receiving efavirenz versus other regimens (P>0.5). In unweighted multivariable-adjusted models, use of efavirenz was associated with a lower risk of depression (GEE AOR 0.51; 95% CI, 0.31-0.82; Cox AOR 0.58; 95% CI, 0.38-0.90) and was not associated with SI (GEE AOR 0.60; 95% CI, 0.29-1.24; Cox AOR 0.50, 95% CI 0.23-1.10). Models weighted for time-dependent confounding showed attenuated effect sizes for both depression (MSM AOR 0.85; 95% CI, 0.51-1.41) and SI (MSM AOR 0.98; 95% CI, 0.52-1.83). Results were qualitatively similar with exclusion of participants with baseline depression and SI, tuberculosis, and pregnancy.

Conclusions: We did not identify an association between efavirenz use and increased risk of depression or SI in southwestern Uganda. These tolerability data support use of efavirenz as a first-line agent in the region. Future work should investigate whether genetic or environmental factors might account for region-specific differences in efavirenz tolerability.

Table. Estimates of the effect of efavirenz on depression and suicidal ideation

<table>
<thead>
<tr>
<th>Model</th>
<th>Depression</th>
<th>Suicidal ideation</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>P</td>
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<tr>
<td>Adjusted GEE</td>
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<tr>
<td>Adjusted Cox</td>
<td>0.58 (0.38-0.90)</td>
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<tr>
<td>Weighted MSM</td>
<td>0.73 (0.43-1.23)</td>
<td>0.23</td>
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</tbody>
</table>
 Timing of Postdischarge Follow-Up and Medication Adherence Among Heart Failure Patients

Leslie L. Chang, Haolin Xu, Adam D. DeVore, Roland Matsouaka, Clyde Yancy, Gregg C. Fonarow, Larry Allen, Adrian F. Hernandez
American Heart Association Young Investigator Database Seed Grant

Background: Prior studies have demonstrated the importance of medication adherence to evidence-based guideline-directed medical therapies (GDMT) in improving outcomes of heart failure (HF) patients. However, adherence rates remain low, with most studies demonstrating a 40-60% adherence to medications. The post discharge transition from hospital to home may be a vulnerable period for HF patients and a delayed outpatient follow-up was previously found to be associated with worse outcomes. In this study, we hope to identify a modifiable factor to improve HF medication adherence rates. We hypothesized that in a population of HF patients, early follow-up is associated with higher rates of medication adherence.

Methods: We analyzed data from Get With The Guidelines-HF linked to Medicare claims. Patients were ≥65 years with HF discharged alive between April 2006 and October 2012. We categorized patients into 4 groups by timing of the first follow-up visit: ≤1 week, 1-2 weeks, 2-6 weeks, and >6 weeks and examined adherence to 5 guideline-directed medical therapies at 90-days and 1-year post discharge: ACE-inhibitor or ARB, evidence-based beta-blockers, aldosterone receptor antagonists, hydralazine/isosorbide dinitrate, and anticoagulants. We defined adherence as a proportion of days covered of greater than 80% for eligible patients discharged on a given therapy. Through mixed-effects logistic regression modeling, we compared the medication adherence of each follow-up group referenced to the earliest follow-up group.

Results: Of 9,878 HF patients in the analysis, 73% had a left ventricular ejection fraction ≤40%, the median age was 78 years (25th to 75th percentile, 71-84), 48% were male, and 75% were white. Overall, 30% of the population had a follow-up appointment within 1 week after discharge and 25% >6 weeks. At 1 year, >80% PDC was as follows: 53% for evidence-based beta-blockers, 48% for ACEi/ARBs, 36% for aldosterone antagonists, 40% for anticoagulants, and 8% for hydralazine/isosorbide dinitrate, with marginally higher rates at 90 days. We found no significant association between timing of first follow-up visit and medication adherence at 90 days (odds ratio [OR], 0.97 [95% CI, 0.88-1.07]) and 1 year (OR, 1.04 [95% CI, 0.92-1.17]) when comparing those with follow-up visits >6 weeks to those with the earliest follow-up visits.

Conclusions: In post discharge HF patients, rates of adherence to GDMT were low and improved transition of care through early follow-up was not associated with increased medication adherence. Future studies are necessary to identify interventions that can improve adherence in HF patients.
Best Strategies for Mobile Health Application Development and Diabetes Management

Curry Cheek, Dr. Rowena Dolor, Dr. Kevin Schulman

Background: We assessed mobile health applications for diabetes to understand current approaches and highlight opportunities for more impactful behavior change approaches in next-generation apps.

Methods: We screened Android store apps that appeared after using the “diabetes” search term meeting the following criteria: English text, for human patients, and no target market outside the United States. App descriptions and screenshots were used to categorize health factors and engagement methods. Surveys were sent to primary care physicians and marketing professors to generate a best practices framework for app development. Participants ranked each engagement method. We assessed interrater agreement using the kappa statistic. We compared this framework to apps for diabetes by analyzing apps using descriptive statistics for engagement methods and health factors.

Results: A total of 191 apps met the screening criteria. Total percentages for any apps with engagement methods in the following domains were social support (7%), self-monitoring (47%), reinforcement tracking (4%), goal setting (4%), and other (49%). Surveys were completed by 26 primary care physicians and 5 marketing professors. We found significant differences between approaches used by Android apps and approaches recommended by experts. Both groups suggested that social support, goal setting, progress tracking toward a goal, and social referencing had the potential to impact 26% to 50% of the population, but only social support and goal setting were used by available apps.

Conclusions: Given differences between theories of engagement and practices in the app market, there are significant opportunities for future research and app development.
Impact of Polyvascular Disease on Patients with Atrial Fibrillation: Insights from Rivaroxaban versus Warfarin in Non-valvular Atrial Fibrillation (ROCKET AF)

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Background: Atherosclerotic disease has a strong association with atrial fibrillation (AF). However, the management of patients with concomitant disease is challenging given the competing risks of cardiovascular and bleeding events. While atherosclerotic disease is prevalent in patients with atrial fibrillation, the long-term outcomes associated with the degree of atherosclerotic involvement are unknown.

Methods: We analyzed outcomes for all patients with carotid occlusive disease, peripheral artery disease, or coronary artery disease randomized in ROCKET AF. Single-bed vascular disease was defined as involvement of only one of these territories; polyvascular disease included patients with involvement of 2 or more vascular beds.

Results: In ROCKET AF, 655 patients had polyvascular and 3,391 patients had single-bed vascular disease. At baseline, patients with vascular disease were more likely to be male, have a higher CHADS2 VASC score, and have a history of congestive heart failure, diabetes mellitus, COPD, and aspirin use. Compared to patients without vascular disease, a higher risk of the composite of stroke, systemic embolism (SE), myocardial infarction, and vascular death was seen in those with single-bed vascular disease (HR 1.68, CI 1.44-1.83, p<0.0001) and polyvascular disease (HR 1.98, CI 1.62-2.42, p<0.0001). Event rates show a trend toward higher risk of cardiovascular events and mortality with increasing vascular bed involvement. For efficacy outcomes, rivaroxaban versus warfarin risk relationships were consistent across vascular disease groups, but use of rivaroxaban was associated with higher rates of major bleeding in patients with single-bed vascular disease (HR 1.27 CI 0.98-1.67) and polyvascular disease (HR 2.23 CI 1.32-3.78) (p for interaction = 0.0025). This risk was primarily driven by non-fatal mucosal bleeds. Baseline aspirin use was consistently associated with increased risk of major and non-major clinically relevant bleeding for all levels of vascular disease.

Conclusions: Compared to those without vascular disease, AF patients with single-bed or polyvascular disease are at higher risk for cardiovascular events. Overall event rates suggest increasing risk with the degree of symptomatic vascular involvement. Further studies are needed to evaluate if these patients would benefit from novel therapies or treatment strategies.
Timing and Frequency of Sinus Surgery are Associated with Lung Transplant Outcomes in Cystic Fibrosis Patients

Tracy Cheng, Adam Honeybrook, Kevin Choi, Alice Gray, Laurie Snyder, Scott Palmer, Ralph Abi Hachem, David W. Jang
OHNS T32 Training Fellowship

Background: Lung transplantation has revolutionized the treatment of patients with end-stage pulmonary disease due to cystic fibrosis. However, transplant rejection remains a major cause of mortality, and rejection rate is often higher in cystic fibrosis patients. Concurrent chronic infection in the paranasal sinuses is common in the cystic fibrosis population, and some attribute the higher rejection rate to sinus infections seeding the lung transplant. Therefore, sinus surgery is frequently performed in these circumstances. Yet, there has been debate in the current literature over whether sinus infections and surgery impact lung transplant survival outcomes.

Methods: This is a single-institution retrospective study of all patients who underwent lung transplantation for cystic fibrosis from 2005 to 2015 at Duke University Hospital based on the United Network for Organ Sharing database. Bivariate analyses were performed to determine whether timing and frequency of sinus surgery, polyp status, radiographic score, and otolaryngologic consultation influenced survival rates after transplant.

Results: A total of 144 patients underwent lung transplantation in the study period. The three-year mortality was 27.4%. 42 patients underwent pre-transplant sinus surgery, 23 underwent post-transplant surgery, and 17 had both pre and post-transplant sinus surgery. The pre-transplant surgery group had a greater three-year survival compared to the post-transplant surgery group (p=0.011). A higher frequency of peri-transplant sinus surgeries was also associated with greater survival (p=0.029). Otolaryngologic consultation at institution of transplant, polyp disease, and radiographic score were not associated with survival.

Conclusions: These findings suggest that the timing and frequency of sinus surgery may influence lung transplant outcomes in patients with cystic fibrosis. However, these findings also suggest that otolaryngologic consultation as well as severity of sinus infection may not affect survival outcomes after lung transplantation. This complicates the question of whether otolaryngologists should be routinely consulted for cystic fibrosis patients under consideration for lung transplantation. Furthermore, otolaryngologists may need to consider parameters other than disease severity to determine whether the patient would benefit from sinus surgery. The role of otolaryngologists and sinus surgery in cystic fibrosis patients with lung transplantation needs to be better elucidated in a prospective study.
Physician Recommendations and Patient Preferences:  
A Qualitative Analysis of the Contralateral Prophylactic Mastectomy Decision

Vinay Choksi, Peter Ubel, Allison Kratka, Kelly Davis, Vanessa Dickerman,  
Mara Buchbinder, Christine Kirby, Sarah Hawley, Karen Sepucha,  
Mike Sabel, Michelle Specht, Clara Lee

**Background:** Over the last two decades, a growing number of women with unilateral breast cancer have chosen to have a contralateral prophylactic mastectomy (CPM), despite guidelines recommending against it for patients without a high risk of second cancer. This qualitative study examines how physicians and patients communicate about the procedure.

**Methods:** Surgeons and patients from 3 academic centers were recruited. We audio-recorded the first surgical consultations of patients, who had early stage unilateral breast cancer or ductal carcinoma in situ, and no strong family history or known BRCA mutation. We read transcripts of the recordings, identified CPM discussion, and coded for communication behaviors relevant to the CPM decision.

**Results:** 26 patients and 6 surgeons participated. Three paths of communication behaviors dominated. In the first (n=12), there was no CPM discussion by the physician or patient, and the patient was not scheduled for CPM at the end of the visit. In a second path (n=8), the physician recommended waiting for genetic testing or imaging results before making a decision about CPM and the patient did not indicate a CPM preference. These patients delayed both CPM discussion and decision until later visits. In the third path (n=4), patients already had an initial preference in favor of CPM. They consistently cited fears of breast cancer recurrence and daily worry of future breast cancer risk as reasons they wanted CPM. They were all scheduled for CPM, regardless of physician recommendation.

**Conclusions:** Initial patient preference for CPM strongly affected the CPM decision. Also, physician recommendations to wait for further medical information influenced the process. Future research should work to identify how patients’ form pre-visit preferences as well addressing these preferences during the initial surgical consultation.
Simultaneous Integrated Parametrial/Sidewall Boosts for Cervical Cancer: Late Toxicity and Outcomes

Lori-Ann Daley, Oana Craciunescu, Gita Suneja, Kim Light, Anna Rodrigues, Junzo Chino

Background: Standard therapy for locally advanced cervical cancer consists of pelvic external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) with concurrent cisplatin-based chemotherapy. For bulkier Stage IB-III disease the pelvic recurrence rate is up to 50%, and over 50% of treatment failures are secondary to disease progression including the para-aortic region and the parametrium. There is increasing interest in improving outcomes with intensity-modulated radiotherapy (IMRT). IMRT with simultaneous integrated boosts (SIB) allows for inhomogeneous dose escalation to a subvolume, while sparing organs at risk such as bowel, bladder, and rectum. However, there is little data on the specific use of SIB to boost the parametria and pelvic sidewalls.

Methods: In this IRB-approved retrospective study, women with intact cervical cancer treated in a single institution with definitive chemoradiotherapy and brachytherapy (BT) boost from 2011-2016 were identified. Involved sidewalls and parametria were treated at 2.1-2.4 Gy per fraction via SIB technique, while the central disease and elective volume was treated at 1.8 Gy per fraction. Acute and late toxicities (defined by CTCAE v 4.0), recurrences (local, sidewall, and distant), and overall survival were analyzed via the Kaplan Meier method.

Results: Forty-three women with bulky stage IB1-IVB cervical cancer were included. All women received whole pelvic radiotherapy (45-51.4 Gy/ 24-25 fractions) as well as parametrial boosts (53.6-60 Gy/ 24-25 fractions) via SIB technique. Median follow-up was 25.2 months. Rates of acute grade ≥2 gastrointestinal (GI), genitourinary (GU), and hematologic (heme) toxicities were 39.5%, 7.0%, and 55.8% respectively; acute grade ≥3 toxicities were 7.0%, 2.3%, and 16.3% respectively. There were no acute grade 4+ toxicities. Two-year rates of late grade ≥2 GI and GU toxicities were 33.5% and 10.4% respectively; two-year late grade ≥ 3 toxicities were 12.0% and 6.2% respectively. There were two rectovaginal fistulas. Two-year overall survival and local control were 82.1% and 89.4% respectively. Cumulative rectal D2cc EQD2 dose ≥75Gy was also associated with late grade ≥ 3 GI and GU sequelae vs <75Gy (66.7% vs. 2.5%, p=0.001 and 66.7% vs. 0%, p=0.004, respectively).

Conclusions: IMRT-SIB is a feasible technique allowing for dose escalation to the parametria and sidewall, with overall toxicity rates similar to conventional techniques. Late GI toxicity appears to be highly dependent upon cumulative rectal dose including brachytherapy. When rectal D2cc was <75Gy EQD2, toxicity rates were low.
Comparing Kinship and Foster Care in NC: The Child Abuse Medical Provider Perspective

Sabrina M. Darwiche, MPH, Lindsay Terrell, MD, Ashley Skinner, PhD, Aditee Narayan, MD, MPH

Background: Guided by federal and state regulations, children in North Carolina (NC) removed from their homes because of allegations of maltreatment are preferentially placed in kinship care. Kinship care’s definition is variable, with NC moving towards using the term to exclusively refer to a care arrangement in which the Department of Social Services (DSS) has taken custody of a child and placed them with a family member or friend, as opposed to foster care, in which a child in DSS custody is placed with a licensed foster parent previously unknown to that child. Although national research is inconsistent as to which form of placement leads to better outcomes for children, there is concern that children in kinship care receive less formal support.

Objectives: To investigate from the perspective of child abuse medical experts practicing in NC: 1) their understanding of the state’s kinship care system; 2) the health needs of children in kinship care vs. foster care; and, 3) how multidisciplinary stakeholders can better work together to serve children in kinship care.

Methods: A mixed method design was used to conduct semi-structured interviews with child abuse medical providers. Data were coded with a team generated codebook. Qualitative data were analyzed in ATLAS.ti 7.5.10, and quantitative data was analyzed in R version 3.2.3.

Conclusions: Major themes included: 1) providers have a foundational understanding of the NC kinship care system, but pockets of uncertainty mark this knowledge; 2) children in kinship care and foster care have equivalent, elevated health needs, but children in kinship care may not receive the same level of care, particularly in terms of their mental health; 3) social workers and medical professionals can make individual and structural changes to improve the ability of the multidisciplinary team to facilitate the health of children in kinship care compared to foster care.
In vivo measurement of time-dependent stress recovery
in tibiofemoral cartilage after exercise-induced strain

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**Background:** Our understanding of cartilage biomechanics carries important implications for the study and management of osteoarthritis, the leading cause of disability in the United States. Study of articular cartilage behavior *in vivo* has been limited by an inability to access this thin joint tissue non-invasively, resulting in many assumptions about human cartilage behavior *in vivo* that are based on explants, animal models, and mathematical modeling. Here, we tested a novel means of observing cartilage biomechanical behavior with reference to stress applied to tibiofemoral cartilage through exercise and the resultant stress recovery of the cartilage – data that has never been observed *in vivo* and that will help synthesize our understanding of cartilage as a porous biphasic material.

**Methods:** With IRB approval, we recruited three male subjects who self-reported neither a history of chronic lower extremity pain, nor lower extremity injury requiring medical intervention. In brief, subjects underwent a 45-minute – 1-hour supine relaxation period, and baseline T2 and DESS MRI scans of their right knees. Subjects then walked at a Froude number of 0.25 for 30 minutes immediately prior to five serial DESS MRI scans paced at approximately every 10 minutes. Cartilage and bony contours were manually segmented under the supervision of musculoskeletal radiologists using 3D modeling software. For each subject, analysis of cartilage thickness at each time-point was performed with reference to the baseline cartilage thickness, and resultant strains were tabulated at each timepoint. Statistical analysis was then carried out with a threshold for significance of \( p \leq 0.05 \).

**Results:** Total initial strain across the tibial cartilage averaged -7.3%, and on average, near full recovery was achieved within 50-60 minutes. Strain at each time-point was fitted to model exponential decay, with a resultant \( p \leq 0.01 \), and Spearman’s correlation coefficient, \( R = -0.90 \).

**Conclusions:** In conclusion, cartilage recovery from exercise induced strain fits the paradigm of poroelastic material behavior that has been described *ex vivo* and in mathematical models. In addition, this method of non-invasive cartilage observation is both valid and may prove useful in future study of *in vivo* cartilage behavior. This study has the potential to open up a new avenue for non-invasively observing cartilage behavior, hopefully leading to earlier diagnosis and prevention of osteoarthritis in the future.
Use of continuous glucose monitors to normalize hemoglobin A1C for individual non-glycemic factors in adults with type 1 diabetes

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3rd Year Research Scholarship

Background: The hemoglobin A1C assay (A1C) provides a convenient reflection of long term glycemic control and vascular complications and has therefore come to play a key role in the clinical management and evaluation of patients with diabetes. Mean red blood cell age (MRBC) is a non-glycemic determinant of A1C that varies enough from person-to-person to impact the clinical interpretation of A1C. We sought to validate and demonstrate the clinical utility of a normalized A1C, nA1C, adjusted for MRBC calculated via a previously described model of hemoglobin glycation.

Methods: A total of 163 subjects with continuous glucose monitors (CGM), including 157 patients with type 1 diabetes, and were followed over the course of 10 months. A previously published model of A1C in terms of CGM glucose levels over a 106 day period and mean red blood cell age (MRBC) over that period was used to estimate MRBC. This MRBC served as a correction factor for future A1Cs, allowing for the calculation of normalized A1C (nA1C). The comparative ability of nA1C and A1C to estimate chronic glycemia as measured by CGM-average glucose, expressed in units of A1C, CGM-A1C, was assessed.

Results: There were 79 patients with a total of 157 A1C and nA1C values paired with CGM-based estimates of glycemia on two separate occasions or more. The median absolute difference between nA1C and GCM-A1C was significantly lower than that between A1C and CGM-A1C (0.34% vs. 0.47 %, p=.001). nA1C was less likely to differ from CGM-A1C by more than 1% than was A1C (8.5% of cases vs. 17.9% of cases). Compared with A1C, nA1C demonstrated improved sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios in determining if CGM-A1C is greater than 7% and if CGM-A1C is greater than or equal to 6.5%.

Conclusions: In a clinical population of patients with type 1 diabetes and CGM data, the test characteristics and clinical utility of future A1Cs can be improved by adjusting for non-glycemic factors as determined by past A1Cs and CGM data.
Alpha-cell regulation of insulin secretion: diverse signals and mediators

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Background: Type 2 diabetes (T2D) is largely driven by insufficient insulin secretion due to β cell dysfunction, resulting in hyperglycemia. Thus, understanding the regulation of insulin secretion is central to developing effective treatments. Most β cell research focuses on glucose as the systemic signal for insulin release. However, this approach may be too simple, ignoring both other nutrient stimuli and local, paracrine signaling from other islet cells. We have demonstrated that amino acids (AAs) robustly stimulate insulin secretion indirectly, through actions regulated by α cells. AA potentiation of insulin release from β cells is mediated by both glucagon and glucagon-like-peptide (GLP-1), two α cell products. We therefore propose that disruption of α-to-β cell communication impairs insulin release after a mixed nutrient meal, resulting in impaired glucose tolerance that propagates hyperglycemia.

Methods: To study glucagon signaling in the β cell, we generated β-cell-specific glucagon receptor (GCGR) knockout mice (β-gcgr KO). We performed in vivo phenotyping studies of the mice to assess glucose tolerance, and then isolated islets to test insulin secretion in response to various insulin secretagogues ex vivo with islet perifusion.

Results: β-gcgr KO and WT controls had similar fasting and refed glucose concentrations and response to intraperitoneal or oral glucose tolerance tests. However, β-gcgr KO mice had impaired glucose tolerance after a mixed nutrient meal. In isolated, ex vivo perifused islets, exogenous glucagon stimulated insulin secretion at high but not low glucose levels; the response at high glucose was not impacted by loss of GCGR. Interestingly, antagonizing the GLP-1 receptor (GLP-1R) in WT islets with exendin-9 (Ex9) severely blunted the insulinotropic actions of glucagon, suggesting that glucagon regulates the β cell through the GLP-1R. Next, we induced glucagon secretion from the α cell by stimulating perifused islets with the AAs glutamine or arginine. In WT islets, neither AA stimulated insulin secretion at low glucose, similar to exogenous glucagon, but did potently increase insulin secretion at high glucose. Antagonizing the GLP-1R with Ex9 greatly reduced AA-stimulated insulin secretion in WT islets, and completely blocked insulin secretion in β-gcgr KO islets. These results demonstrate the importance of both the GLP-1R and GCGR in β cells for the insulin response to AAs. Finally, WT islets incubated in hyperglycemic conditions showed ~40% reduction in both GCGR and GLP-1R levels, demonstrating that diabetic conditions can reduce α-to-β cell communication by decreasing the expression of both receptors.

Conclusions: Our findings highlight a critical role for α cell products in regulating β cell function in response to AAs. Interrupting α-to-β cell communication by genetic elimination of GCGR or pharmacological blockage of GLP-1R impaired glucose tolerance following a mixed nutrient meal in vivo and blunted insulin secretion in response to AAs in perifused islets. Glucotoxic conditions replicating a diabetic environment reduced islet expression of both GLP-1R and GCGR in WT islets. This suggests that α-to-β cell communication may be impaired in T2D, decreasing insulin secretion following mixed nutrient meals and potentially contributing to diabetic hyperglycemia. Understanding of α-to-β cell relationships is likely to guide novel targets to improve glucose homeostasis for the treatment of T2D.
Patterns and Predictors of Pain following Lung Transplantation

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**Background:** Thoracic surgery, including lung transplantation, is associated with significant post-operative pain. However, few studies have examined variability in pain levels following lung transplantation, or examined individual differences influencing changes in pain.

**Methods:** We performed a retrospective study of a cohort of 150 patients transplanted and discharged from Duke University Hospital between January 2015 and September 2016. During hospitalization and at clinic visits up to two months after discharge, subjective pain ratings were obtained using a 0-10 Numeric Rating Scale. Psychiatric diagnoses, medical and surgical variables, and Center for Epidemiological Studies – Depression (CES-D) scores collected before and after hospital discharge were examined as predictors of post-surgery pain.

**Results:** During hospitalization, pain ratings decreased over time (p<.001). Predictors of higher pain levels included pre-transplant history of depression (p=.001) and anxiety (p=.04), bilateral lung transplant (p=.01), and lower six-minute walk distance (p<.001). Two months after discharge, 18% of patients reported continued pain and 34% remained on opioid pain medications. Elevated CES-D scores (p=.002), more frequent post-operative complications (p=.03), and greater opioid use (p=.009) predicted higher pain levels 2-months post-discharge.

**Conclusions:** We conclude that patients with psychiatric comorbidities may be at risk for greater pain, and may require additional strategies for more effective pain management.
Stromal Interaction Molecule 1 (STIM1) is required for normal uterine contraction and is altered in obesity

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Background: Appropriate regulation of uterine contractility is necessary for successful parturition; inadequate uterine contraction is associated with prolonged labor, need for induction/augmentation, and cesarean delivery. Maternal obesity (BMI ≥30) increases the risk of obstetric complications secondary to poor uterine contractility. The mechanisms by which obesity affects myometrial contractility are unknown. Stromal interaction molecule 1 (STIM1) is a single-pass transmembrane protein that functions as a calcium (Ca²⁺) sensor by activating store-operated Ca²⁺ (SOC) channels on the plasma membrane. STIM1 is required for maintaining both cytoplasmic and mitochondrial Ca²⁺ homeostasis and has been implicated in both excitation-contraction (EC) coupling and metabolic regulation. To date, the role of STIM1 in uterine smooth muscle remains unknown. Herein, we characterize the role of STIM1 in the normal myometrium and begin to examine whether STIM1 function is altered in obesity.

Methods: STIM1-LacZ reporter mice underwent timed matings; uterine horns were isolated for histological and biochemical analysis. To assess contractility, uterine horns were harvested from STIM1-deficient (STIM1⁺⁻; STIM1⁻⁻) mice and myometrial strips were suspended in a tissue organ bath and stimulated with increasing doses of oxytocin. Parallel experiments were performed in both non-pregnant (NP) and term-pregnant (TNL) wild-type (WT) C57Bl/6 mice; muscle strips were pre-treated with a SOC channel inhibitor or vehicle control prior to stimulation with oxytocin. A myometrial-specific STIM1 knockout mouse (PR-Cre⁺⁻/STIM1fl/fl) was developed to assess myometrial contractility in vivo. Human myometrial expression was measured in uterine biopsy samples obtained from term-pregnant women undergoing cesarean delivery at DUMC.

Results: STIM1 is expressed in both the murine and human myometrium; STIM1 expression is upregulated in pregnancy and remains elevated throughout gestation and immediately post-partum. In myometrial strips isolated from NP and TNL mouse models, STIM1 is required for synchronous and sustained uterine contraction. Both STIM1 deficiency and SOC channel inhibition result in decreased contractile force, reduced contraction frequency, and diminished basal tone in response to myogenic (spontaneous) and oxytocin-induced stimulation. Preliminary data in both WT and STIM1-deficient mouse models suggests STIM1 expression is altered in obesity and that STIM1 deficiency results in reduced mitochondrial Ca²⁺ stores leading to a Ca²⁺-related block in oxidative metabolism.

Conclusions: We have demonstrated that STIM1 is required for a normal contractile phenotype in the myometrium. Our preliminary results suggest STIM1 as a potential link between obesity and myometrial contractility. Further studies are required to investigate this relationship, as understanding the effect of obesity on uterine contractility would lead to improved maternal and perinatal outcomes.
Wound Infiltration with an Elastomeric Pump for Analgesia after Cesarean Delivery: A Randomized Controlled Study

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Background: Cesarean Delivery (CD) is one of the most common surgical procedures performed in the United States and worldwide. Even with multimodal analgesia after CD, nearly one-fifth of women report severe postoperative pain, which can adversely affect both mothers and their newborns. The addition of local infiltration to the current standard analgesic regimen may offer a way to improve postoperative analgesia. Therefore, we performed this study to determine if the addition of continuous local anesthetic wound infiltration using an elastomeric pump would improve pain scores and decrease opioid consumption after CD.

Methods: Following IRB approval and informed consent, American Society of Anesthesiologists physical status II and III women scheduled to undergo primary or repeat CD were randomized to receive wound infiltration with a continuous infusion of either ropivacaine plus ketorolac or placebo after administration of a standardized anesthetic technique that included intrathecal morphine. All patients received a standardized multimodal postoperative analgesic regimen that included regular acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), as well as opioids as needed for breakthrough pain. Pain scores, opioid consumption, and incidence and severity of side effects were recorded at 2, 24, and 48 hours postoperatively. Data were assessed for normality and analyzed using t-tests or Wilcoxon Rank Sum tests as appropriate for numeric data, or chi-square or Fisher’s exact test as appropriate for dichotomous data. Time to first rescue medication was analyzed using Kaplan-Meier mean time to event analysis.

Results: A total of 22 women were enrolled in the study, 11 each in the treatment and placebo groups. There were no significant differences between the two groups with respect to pain scores, opioid consumption, or side effect profile, at any time point. There was also no significant difference in the time to first rescue medication between the two groups.

Conclusions: These results suggest that the addition of a continuous infusion of local anesthetic plus NSAID does not confer an additional benefit to postoperative analgesia in the setting of intrathecal morphine use and a multimodal postoperative analgesic regimen. The results of this study should be interpreted cautiously, however, due to the small sample size.
Shared Medical Appointments for Prenatal Care: Maternal and Neonatal Health Outcomes

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**Background:** Traditionally, prenatal care is delivered through a series of individual appointments. However, studies have demonstrated maternal and neonatal health benefits to participation in group prenatal care. Most studies of group prenatal care evaluate the Centering Pregnancy model, which places women in set groups for the duration of their pregnancy and follows a specific educational curriculum. Shared Medical Appointments (SMAs) bring together patients with similar health concerns for group medical visits. Compared to Centering Pregnancy, SMAs represent a more flexible, but less structured, method of delivering group prenatal care. Our study sought to determine whether participation in prenatal SMAs affects neonatal and maternal health outcomes, a topic largely unexplored in the literature.

**Methods:** Myers Park OB-GYN clinic is a training site for Carolinas Healthcare System OB-GYN residents. It is located in Charlotte, North Carolina and serves a racially, ethnically, and socioeconomically diverse population. SMAs for prenatal care were offered at Myers Park between July 2014 and July 2015 to ease scheduling congestion. Retrospective data were collected for women who obtained prenatal care, either SMA or traditional individual care, during that time period. Demographic, birth, and postpartum data were extracted from the electronic health record (SMA n=78, traditional care n=277). SMA participants were categorized by the percentage of SMA visits (Some SMA: <30% SMA visits; Moderate SMA: ≥30% SMA visits). Logistic regression models were created to assess the effect of SMA participation on maternal and neonatal health outcomes including: cesarean birth, low birth weight, preterm birth, attendance at postpartum appointment, use of highly effective postpartum contraception, postpartum depression diagnosis, and breastfeeding.

**Results:** Of the women who had at least one SMA visit, 52.6% were classified as “Some SMA” and 47.4% were classified as “Moderate SMA”. The unadjusted analysis showed “Some SMA” patients had a lower rate of postpartum visit attendance, compared to patients receiving traditional individual care (OR=0.48, 95% CI: 0.25-0.94). This association remained statistically significant after adjustment (OR=0.48, 95% CI: 0.24-0.94). Neither the unadjusted nor adjusted models demonstrated a statistically significant association between SMA and any of the other maternal or neonatal health outcomes.

**Conclusions:** SMAs for prenatal care can be implemented to ease scheduling congestion without negative impacts on maternal or neonatal health. However, these findings suggest fidelity to a structured model of group prenatal care may be necessary to achieve health outcome improvement.
No-Shows in Adult Urology Outpatient Clinics:
Economic and Operational Implications

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PDC Outcomes Research Team (PORT) Steering Grant

Background: Greater efforts to contain cost and shift to value-based care have become priorities in healthcare. From an administrative perspective, missed appointments cause an underutilization of resources, increase costs, and reduce efficiency. This quality improvement study aims to explore provider-related factors associated with missed appointments for adult urology clinics, using no-show data from electronic health records and scheduling data, and to consider their operational and financial implications on the overall health system. To our knowledge, this is the first comprehensive study of no-shows in adult urology.

Methods: No-show rates were determined using data from electronic health records (EPIC) and scheduling software (CADENCE) of patients scheduled for appointments in adult urology clinics at Duke University Medical Center and Duke Raleigh Hospital between January 2014 and December 2016. For statistical analysis, T-test, Wilcoxon Rank-sum, ANOVA, and bivariate fit tests were employed.

Results: Of 72,571 appointments, 13,219 (18.2%) were no-shows. The no-show rates per provider-related characteristic were: provider type (physician, 22.1% vs advanced primary provider, 34.0%), visit category (new, 26.9% vs return, 25.6% vs procedure, 17.5%), faculty status (assistant, 22.9% vs associate, 21.9% vs professor, 21.4%), and specialty (oncology, 26.7% vs reconstructive, 22.9% vs stones, 25.4%). Average lead times (time a patient can book in advance of his or her appointment) of advanced primary practitioners (APP) and physicians were 47 and 62 days respectively. There was a statistically significant difference in no-show rates by provider type (p<0.01) and new patient no-show rates by provider type (p<0.01). However, there was no statistical difference in rates by specialty, faculty status, provider bump history, provider-based visit types, and average lead time. The potential loss in revenue from outpatient no-shows at our institution ranged from $1.3-1.4 million annually.

Conclusions: Provider type and new patient visits by provider type have statistically different no-show rates. Missed appointments are costly and affect clinical efficiency, access to care, and potentially patient outcomes. Given the shift towards value-based care and future changes to the urology workforce, further investigations are needed to determine interventions to help reduce no-show rates. As in the airline industry, models to predict and adjust clinics accordingly should be developed and deployed.
Respiratory Polyomaviruses and Pediatric Illness in Singapore

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Duke NUS Startup Funds

Background: Although WU polyomavirus (WU) and KI polyomavirus (KI) have been demonstrated to infect the human respiratory tract, it remains unclear WU or KI cause human disease. This cross-sectional study of general pediatric patients in Singapore sought to further investigate the relationship between WU and KI infection and respiratory disease.

Methods: Upon consent, residual respiratory samples from pediatrics inpatients previously screened for common respiratory viruses were collected and further screened for WU and KI using qPCR. The amplicons of positive samples were sequenced for confirmation. The severity of a patient’s illness was assessed by chart review post-discharge looking for clinical markers of respiratory status such as presenting symptoms, diagnoses, and interventions.

Results: From December 2016 to April 2017, 201 patients with residual respiratory samples were enrolled in the study. The average age of all participants recruited was 45.1 months. WU and KI were detected in 13% (26/201) and 3% (6/201) of patients, respectively. SARI patients with a WU monoinfection were more likely to require IV hydration than those without a WU or KI infection. We identified no other significant differences between patients with evidence of KI or WU infection and SARI patients without such evidence.

Conclusions: Our data do not support the hypothesis that molecular evidence of WU is associated with increased morbidity among general pediatric patients with SARI in Singapore.
Patient-Reported Disease Activity and Adverse Pregnancy Outcomes in Systemic Lupus Erythematosus and Rheumatoid Arthritis

Nathaniel Harris, PhD, Amanda Eudy, PhD, Megan Clowse MD, MPH

Background: Patient-reported measures of disease activity may provide useful adjuncts to physician-reported measures in identifying pregnancies at greater risk for adverse pregnancy outcomes. Little is known about the utility of these measures in SLE patients, and most analyses in patients with RA use only a single measure of disease activity or disability.

Methods: Data on pregnancy outcomes were collected on 225 patients with SLE or RA enrolled in a prospective registry at a single academic center from 2008-2016. Disease activity was measured by physician global assessment (PGA) in SLE and RA, as well as joint counts in RA. The primary patient-reported measure used was the Health Assessment Questionnaire (HAQ); we also tested the utility of pain and general health visual-analog scales. Univariate and multivariable regression models adjusted for race, education, living status, and BMI were used to assess the relationship between patient and physician-reported measures of disease activity and adverse pregnancy outcomes.

Results: Among 145 women with SLE, the mean age was 30 and 50% were African American. Among the 80 women with RA, mean age was 33; nearly 80% were white. Women with RA were more likely to be living with a spouse or partner (85% vs 68%) and were more likely to have completed at least 4 years of college (75% vs 52%). Nearly 50% of women with lupus were Ro+, and 17% percent had a history of lupus nephritis. In women with RA, patient-reported disease activity was associated with preterm birth (OR 5.9 (95% CI: 1.5-23.9)), and gestational age (beta -1.5 weeks (-2.6, -0.4)). In addition, physician assessment of disease activity predicted preterm (OR 2.1 (1.2-3.5)) and small for gestational age births (OR 1.8 (1.03-3.1), and gestational age in weeks (beta -0.6 weeks (-0.9, -0.02)). On the other hand, for women with SLE, patient-reported measures, including HAQ, pain and global health, were not associated with adverse pregnancy outcomes. However, physician’s global assessment was associated with preterm birth (OR 2.9 (1.6-6.3)), C-section delivery (OR 2.3 (1.0-5.3)), and preeclampsia (OR 2.8 (1.3-6.3)) in SLE patients. The results do not appear to be driven by nephritis or aPL syndrome.

Conclusions: Patient-reported measures of disease activity in RA patients may provide useful adjuncts for physicians to identify pregnancies at higher risk for adverse events. This suggests that increased activity on a patient-reported measure should prompt action during an RA pregnancy. In contrast, in SLE, while the physician-reported measures correlated with pregnancy outcome, the patient-reported measures did not. Our findings provide additional support for the use of patient-reported measures among women with inflammatory arthritis in pregnancy, and impetus for the development of patient-reported measures that more accurately reflect lupus disease activity.
ALS Reversals: Demographics, Disease Characteristics, Treatments, and Co-Morbidities

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Background: Amyotrophic lateral sclerosis (ALS) is a devastating and almost universally fatal neurodegenerative disease. Very rarely, a person who appeared to have ALS stops progressing, regains significant motor function, and does not relapse. Studying these “ALS reversals” could uncover an under-recognized mimic syndrome, a genetic mechanism of ALS resistance, or an effective treatment. Here, we compile all known cases of ALS reversals into a database to compare their demographics, disease characteristics, treatments, and co-morbidities to those of patients with more typically progressive ALS.

Methods: Cases of possible ALS reversal were found in prior publications, in the Duke ALS clinic, through self-referral or referral from other Neurologists, and on the internet. Of 83 possible reversals identified, 32 cases were included because chart or literature review confirmed their diagnosis and a robust, sustained improvement in at least one objective measure. Controls were patients with typically progressive ALS in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database and National ALS Registry. Cases and controls were compared using descriptive statistics.

Results: ALS reversals were more likely to be male and have limb onset disease but were less likely to be white. They also were younger and initially progressed faster. The prevalence of myasthenia gravis (MG) in cases (7%, n=2) was higher than estimates of prevalence of MG in the general population (0.03%). The odds of exposure to curcumin (OR=425, p<.0001), luteolin (OR=403, p<.0001), cannabidiol (OR=201, p<.0001), azathioprine (OR=161, p<.0001), copper (OR=29.7, p=.001), glutathione (OR=22.9, p=.005), and vitamin D (OR=6.92, p=.02) were greater for cases than controls.

Conclusions: When compared to patients with typically progressive ALS, patients with reversals differed in their demographics, disease characteristics, and treatments. Our data suggest that ALS reversals warrant further work up for antibody-mediated ALS mimickers, including atypical MG. Treatments associated with multiple ALS reversals deserve further study.
Evaluation of a training program for Indian frontline healthcare providers to improve their supports for patient activation

Sehj Kashyap

**Background:** Healthcare providers play an integral role in supporting patient activation, which refers to patients’ abilities to self-manage their health. In healthcare systems like India, providers do very little in their interactions to activate patients. In this study, we developed a culturally relevant training program for Indian healthcare providers in order to train them on how they could support their patients’ activation during routine clinical interactions. The program was then evaluated on whether it improved providers’ supports for activation.

**Methods:** A training program run by Noora Health for healthcare providers was redesigned for building provider supports for patient activation. An observational, single group pre-test, post-test study design was then carried out to assess whether the training was effective in improving provider support for activation. The study sample consisted of nurses and doctors that had been selected to participate in one of four trainings in the state of Karnataka, India. A questionnaire was used to assess outcomes. The primary outcome was providers’ support of patient activation which was assessed through The Clinician Support for Patient Activation (CS-PAM) measure as well as study-specific attitudinal statements. The secondary outcome was providers’ ability to activate patients—specifically, providing self-management support and judging quality of activation behaviors—which were assessed through two patient vignettes.

**Results:** 125 out of 133 attending healthcare providers were invited to participate in the study, and 113 (90.4%) completed both pre- and post-tests. 106 were nurses, 15 were doctors, and 4 were non-clinical but patient-facing social workers. 28% were males; 72% were females. Median years of medical field experience was 5.25 years and median tenure in the last or current hospital was 2.45 years. Post-training, providers showed a statistically significant median increase in support for patient activation, as measured by the CS-PAM, (+2.53 on 100-point scale, 95% CI .26 to 4.7) $z = 2.257, p = .024$, including a 48% relative increase in number of providers falling into the highly supportive category. 10 out of 12 patient engagement statements showed trend towards improvement, though the differences were not statistically significant. There was a statistically significant median increase in providers prioritizing giving self-management supportive instructions to the patient, (difference of +0.13 on a 6-point scale) $z = 2.889, p = .004$. But, providers did not demonstrate improved recognition of non-activating patient-provider interactions, since difference in appraisal was not statistically significant from baseline for globally, (difference of +.218 on 10-point scale) $z = 1.204, p = .228$, and on specific behaviors, $z = 0.359, p = .720$. Additionally, two attitudinal statements trend in opposite direction, out of which only one was statistically significant, “Teaching patient caregivers about health skills is not a good use of my time,” (difference of -0.33 on 4-point scale) $z = -2.753, p = .006$.

**Conclusions:** This study is among the first of its kind for the Indian provider population and finds that providers can be trained to better support patient activation. Single group pre-/post-test study design limitations apply to interpretation of results.
Open Notes: A Qualitative Study of Oncology Patients’ Experiences Reading their Cancer Care Notes

Neha Kayastha, Kathryn I. Pollak, Thomas W. LeBlanc

Background: Modern electronic medical record systems and patient portals increasingly allow patients direct access to their clinicians’ notes. While it is sometimes assumed that this transparency is inherently good for patients and families, there may be risks inherent in “open notes.” Little is known about cancer patients’ experiences reading their own medical records outside of the primary care setting. We aimed to describe the experience of patients with advanced cancer who read their own cancer care notes.

Methods: We recruited 20 adult patients with metastatic or incurable cancer who were receiving active cancer treatment to participate in semi-structured qualitative interviews. The interviews focused on 4 areas: their overall experience reading notes, how notes affect cancer care experiences, reading a note in real time, and suggestions for improving notes. We used a constant comparison approach to analyze the data.

Results: Four main themes emerged; patients reported that notes: (a) increased comprehension, (b) addressed uncertainty, relieved anxiety, and facilitated control, (c) increased trust, and (d) for a subset, increased anxiety. Patients described increased comprehension, as notes refreshed their memory and clarified their understanding of visits. Notes addressed uncertainty and relieved anxiety, in part because enhanced comprehension mitigated the unfamiliarity of cancer. They facilitated control, empowering patients to ask more questions to clinicians. The transparency of notes also increased the trust patients have in their clinicians. For a subset of patients, however, notes were emotionally difficult to read and raised concerns. Some patients even described a compulsion to read notes that they wished they could not access. Patients consistently identified medical jargon and repetition in notes as areas for improvement.

Conclusions: Our findings suggest that reading notes improves patients’ care experiences overall, though a subset experience increased distress from “open notes.” As reading notes becomes a routine part of the patient experience, it is important for physicians to elicit and address concerns that arise from the notes, further engaging patients in their care.
Supporting Clinical Decision Support: Structured Data and ACR Select Implementation

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**Background:** An electronic health record (EHR) affords the opportunity to introduce clinical decision support (CDS) tools at the point of care that increase care quality and patient safety. Maximizing those tools requires understanding how providers interact with the EHR, including the use of free-text and structured data. *American College of Radiology (ACR) Select*, a CDS tool developed to help ordering providers choose an imaging procedure according to ACR Appropriateness Criteria, uses an algorithm that depends on users selecting from a checklist of structured clinical indications.

**Methods:** Upon implementation of *ACR Select* at Duke Health, data was collected on baseline provider behavior for six months of imaging orders. The authors analyzed the proportion of free-text and structured data entry by hour of order, provider specialty and provider level of training using logistic regression and chi-square tests where appropriate.

**Results:** 53.4% of imaging orders are placed with a free-text clinical indication, thus unable to be scored for feedback by *ACR Select*. Each successive hour in the workday is associated with a 3.2% increase in likelihood on average of providing a free-text clinical indication. Residents and Physician Assistants are more likely to provide free-text clinical indications than faculty Physicians. There is significant difference across specialties in users providing free-text clinical indications. 43% of free-text orders come from an Emergency Department.

**Conclusions:** Lack of structured data entry limits the impact of the *ACR Select* clinical decision support tool on quality of care, patient safety, and efficacy of radiologic exams. A steady decrease in structured entry later in the workday suggests that the interface is not perceived as intuitive or quick. The proportion of free text entry varies by provider specialty, with Oncology subspecialties and Emergency Medicine among the highest, suggesting complexity of patients and time pressure can both affect ordering behavior. Providers across levels of training provide a free-text clinical indication in a majority of orders, and provider education for the CDS tool should be multidisciplinary.
Biological Cross Talk at the Osteochondral Junction: Implications in Osteoarthritis

Hanna Kemeny, Terese Camp, Yang Yong, Nicholas Kwon, Jonathan Riboh

Background: Osteoarthritis (OA) is a leading cause of physical disability in the US. Despite research efforts, the exact pathogenesis of OA remains unknown. OA is increasingly viewed as a “whole joint disease,” including metabolic and structural abnormalities of cartilage, muscle, ligaments, synovial tissue, and subchondral bone. However, one of the big gaps of knowledge is in how these tissues interact in the development of OA. Specifically of interest is the relationship between bone and surrounding cartilage. Bone-driven OA has been linked with abnormalities and injury to the subchondral bone. In order to explore this mechanism, our lab used an in vitro co-culture model to examine the effects of subchondral bone explants from OA patients on three dimensional chondrocyte cultures.

Methods: IRB approval was obtained to collect tissue samples from patients undergoing total knee arthroplasty (TKA) at our institution. Subchondral bone was characterized as “sclerotic” (S) based on visual inspection. Direct Co-Culture: S bone explants (n = 5 patients) were cultured directly with chondrocytes embedded in a 3D fibrinogen gel matrix (n= 30 gel matrices from n= 5 patients) for 72 hours. Indirect Co-Culture: Conditioned media was collected from S bone (n=5 patients), and cultured with 3D chondrocyte fibrinogen gels for 72 hours (n=30 gel matrices from n=5 patients). Conditioned media was screened with an ELISA cytokine array. At the completion of all co-cultures, RNA was extracted from the chondrocytes, and RT-PCR of genes involved in chondrocyte metabolism and OA was performed. Relative expression with respect to GAPDH was calculated for all samples, and differences between untreated and sclerotic groups were calculated using an unpaired t-test.

Results: In the direct co-culture condition, levels of collagen X (fold change 7.1 ± 0.9; p<0.05) and ADAMTS4 (fold change 8.2 ± 3; p<0.05) in chondrocyte gene expression were significantly upregulated with OA bone compared to no bone. Collagen I expression was significantly decreased (fold change 0.2 ±0.1; p>0.05) in chondrocytes exposed to OA bone. Supernatant from NS and S bone contained significantly elevated levels of IL-6 (mean absorbance 2.5; p<0.05) and IL-8 (mean absorbance 2.4; p<0.05) and levels of other inflammatory cytokines (IL1-α, IL-2, IL-10, IFN-γ, TNF-α, etc.) were non-detectable.

Conclusion: Direct co-culture of primary human chondrocytes with arthritic subchondral bone significantly increases the expression in chondrocytes of the aggrecanase ADAMTS4 as well as collagen X, a known marker of chondrocyte hypertrophy and de-differentiation in osteoarthritis. In contrast, type I collagen production is significantly decreased. The expression of sox 9, MMP13, type II collagen and aggrecan were not significantly affected. These effects are similar, though dampened in the indirect co-culture model. The major cytokines found in conditioned media from OA subchondral bone were IL-6 and IL-8. These results suggest that exposure of chondrocytes to diseased subchondral bone has a direct negative metabolic effect, which may be in part mediated by IL-6 and/or IL-8 secreted from bone. Further studies in our laboratory are investigating this relationship.
A novel formulation of niclosamide treats metastatic osteosarcoma in vivo

David Kerr

Background: Osteosarcoma (OS), the most common primary bone malignancy in children, has seen few therapeutic advances in the last three decades. Current therapy for OS includes adjuvant chemotherapy, frequently based on agents that are associated with substantial treatment-related morbidity, such as doxorubicin. As seen with other cancer types, the search for drugs that are effective against OS has revealed a number of agents that appear to be effective in vitro but lack a pharmacokinetic profile useful for treatment of in vivo disease. One such drug is niclosamide, which targets a number of pathways known to be dysregulated in OS, such as the Akt/mTor cell proliferation pathway. However, when given as an oral tablet it has poor bioavailability and requires exceedingly high doses or a solubilizing agent such as DMSO or DMA to achieve a therapeutic response in orthotopic models. Thus, an effective mechanism of delivery for this drug (and similar agents) would mark an important step in providing new treatment options for patients. In this study, we tested a novel formulation for niclosamide, in which an esterified form of niclosamide becomes the pure-drug core within a synthetic, lipid-coated nanoparticle for delivery to OS tumors.

Methods: Western blot analyses and dose response assays were performed on cultured 143B human osteosarcoma cells after treatment with niclosamide-stearate nanoparticles. Nanoparticles were prepared by solvent exchange, precipitating the nanoparticles from acetone solution into an excess of water (1:9 v/v). An in vivo model of metastatic osteosarcoma was generated via tail-vein injection of 1x10^6 143B human osteosarcoma cells into 12-week-old SCID/beige mice. Mice were randomly assigned to 4 treatment groups (n=4 per group) as follows: 1) phosphate-buffered saline (200ul i.v. weekly), 2) niclosamide-stearate nanoparticles (35nm diameter; 200ul of 100uM, i.v. weekly), 3) doxorubicin (1.2 mg/kg i.p. biweekly), and 4) combined therapy. Mice were euthanized when they presented with any signs of morbidity, including lethargy or behavioral changes. Kaplan-Meier survival curves were compared using Log-Rank tests.

Results: In dose response assays, 143B osteosarcoma cells were more sensitive to niclosamide in nanoparticle form than in DMSO solution (IC50 0.24±0.02 vs 1.34±0.13 uM) and the drug markedly reduced the active phosphorylated components of the Akt/mTOR pathway on Western blot analysis. In animal experiments, mice treated only with niclosamide-stearate nanoparticles did not experience any early side effects, though both the doxorubicin-only and combined-therapy groups demonstrated early treatment-related weight loss, and treatment with doxorubicin was held for these groups at day 21. Treatment with the niclosamide-stearate nanoparticles significantly prolonged survival in mice with metastatic osteosarcoma compared to the saline-treated control group (mean 40 vs 30 days, p=0.0067), and there was no significant survival difference between groups treated with niclosamide-stearate nanoparticles, doxorubicin, or combined-therapy.

Conclusions: Niclosamide-stearate nanoparticles appear to be an effective chemotherapeutic agent against metastatic osteosarcoma cells in vivo, with a survival benefit comparable to doxorubicin but without the treatment-related toxicity associated with doxorubicin therapy. This may represent a new modality for treating osteosarcoma in patients with or without known metastatic disease, as well as a potential method for in vivo delivery of other pharmacokinetically-similarly hydrophobic drugs.
Using a Novel Proteomics Approach to Identify mGluR5 Regulatory Proteins In Vivo

Christopher L. Kline, Nicole Calakos
Eugene A. Stead, Jr. Student Research Scholarship

**Background:** Dysregulation of the metabotropic glutamate receptor 5 (mGluR5) has been shown to increase protein translation and cause circuit dysfunction in neurodevelopmental disorders like Fragile X and obsessive compulsive disorder. Utilizing a promiscuous biotin ligase, this project aims to identify novel mGluR5 protein interactions representing potential therapeutic targets for further study.

**Methods:** The technology used for this study allows a view of the local synaptic signaling complex through the fusion of an mGluR5 isoform to a biotin ligase, BirA. The mGluR5-BirA fusion protein was delivered via viral vector injected into the striatum of newborn mice. The BirA enzyme biotinylates proteins within a 10nm radius following subcutaneous injection of biotin. Affinity purification columns were used to pull down biotinylated proteins of interest. A cytosolic and transmembrane BirA were used to control for non-synaptic interactions. Successful expression of the fusion protein was evaluated using polymerase chain reaction (PCR), western blots, and immunohistochemistry. An HA epitope tag on the BirA fusion protein was utilized for this purpose. Qualitative and quantitative mass spectrometry was performed to identify purified proteins for further study.

**Results:** Integration and transcription of the lentivirus vector was confirmed via PCR. Results of streptavidin staining of transfected neuron cultures suggest appropriate function of the fusion proteins. Immunohistochemistry (IHC) for mGluR5b-BirA and both transmembrane and cytosolic BirA constructs in brain slices was successful. Western blots confirmed expression and function of both control constructs, but were less definitive for mGluR5a and mGluR5b fusion proteins. Qualitative mass spectrometry results of affinity column purified proteins are currently pending at time of writing.

**Conclusions:** We have conflicting results from IHC and western blotting regarding mGluR5 construct expression. The successful validation of the transmembrane and cytosolic controls in both mediums suggests our technique was correct. One hypothesis is that the mGluR5-BirA fusion protein is mis-folding and/or is rapidly degraded. The results of the pilot mass spectrometry will help confirm or refute this hypothesis, as we expect a mis-folded protein to be interacting primarily with endoplasmic reticulum or proteasome proteins, as opposed to those found at the synapse. Success of this pilot run will enable further study of novel mGluR5 interactors.
Finding healthcare prices online: how hard is it to be an informed healthcare consumer?

Allison Kratka, Charlene Wong, Peter Ubel

**Background:** The US health system places an increasing emphasis on patient responsibility in containing the cost of care. Patients require easy access to healthcare prices if they are to be cost-conscious consumers. We describe the availability of price information for common medical procedures using search engines.

**Methods:** We conducted systematic Google and Bing searches using the search terms ‘cost of [procedure] in [city]’ for four common procedures in eight US cities. The top two pages of search results were sorted into five categories: Generic Relevant Information, Price Transparency Sites, Single Provider/ Clinic Sites, Quality Only Sites, and Unrelated Sites. We performed chi square analyses to test whether the distribution of categories and availability of prices differed across procedures, cities, search engines, and search terms.

**Results:** 67.5% of the websites examined did not provide any type of price information. Of those that did, only 53.6% were prices relevant to the geographic area queried. Price availability differed by procedure (p<0.001), ranging from 12.6% of results for hip replacement to 44.3% of results for brain MRI. The most common categories of websites were Single Provider/ Clinic (28.4%), Generic Relevant Information (27.6%), and Price Transparency (21.9%). Unrelated Sites made up 17.4% of search results, and Quality Only Sites only 4.7% of results.

**Conclusions:** Price estimates for common medical procedures were infrequently available when using search engines. Price transparency sites, which most often provided prices, were an uncommon top search result. Even when prices are available, they are often irrelevant to the consumer’s geographic area. Consumers need better access to price information if we expect them to be smart shoppers for their healthcare. Policymakers have opportunities to ensure the availability of healthcare prices for consumers, through mandated all-payer claims databases for example, and should do so.
Postoperative Venous Thromboembolism in Children is Increased in Setting of Cancer or Infection

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**Background**: In adults postoperative venous thromboembolism (VTE) is associated with malignancy, trauma, and obesity. Although adult risk factors are often extrapolated to children, age related changes in hemostasis and lower rates of VTE may affect postoperative VTE risk in these patients. Therefore, we examined a national database to identify risks and outcomes of VTE in pediatric surgical patients.

**Hypothesis**: Children would be more likely to experience postoperative VTE following major infections or in the presence of cancer.

**Methods**: The 2012–2013 National Surgical Quality Improvement Program-Pediatric was queried to identify patients (ages 0-18) diagnosed with postoperative VTE. Perioperative outcomes were compared between propensity-matched patients who experienced VTE vs. those who did not using a 2:1 nearest neighbor algorithm. Univariate analysis was conducted using Kruskal-Wallis test for continuous variables and Pearson χ² test for categorical variables. Risk factors for VTE were identified by multivariate analysis.

**Results**: We identified 130 children who developed postoperative VTE. Patients developing VTE had increased median operative time (122.5 min vs. 79) and total length of stay (21.5 days vs. 4) compared to those who did not. In multivariate analysis major infections and active cancer significantly increased VTE risk. Specifically, pneumonia (odds ratio [OR] 1.73, 95% confidence interval [CI] 1.30–2.29, p<0.001), central line-associated bloodstream infection (OR 1.69, 95% CI 1.18–2.42, p<0.001), and sepsis (OR 1.47, 95% CI 1.18–1.82, p<0.001) demonstrated increased likelihood of VTE. Cancer also demonstrated significant risk for postoperative VTE (OR 1.30, 95% CI 1.08–1.58, p=0.01).

**Conclusions**: Malignancy and systemic infection increase postoperative VTE risk in children. These findings should prompt consideration of prophylactic anticoagulation in the appropriate clinical setting. Further studies investigating the biology underlying VTE risk in children are needed.

**Table**: Independent risk factors for venous thromboembolism in postoperative pediatric patients.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P-value</th>
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<tr>
<td>Pneumonia</td>
<td>1.73</td>
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<td>Central Line Associated Bloodstream Infection</td>
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<td>1.18</td>
<td>2.42</td>
<td>&lt;0.001</td>
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<td>Sepsis</td>
<td>1.47</td>
<td>1.18</td>
<td>1.82</td>
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<tr>
<td>Cancer</td>
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<td>Abscess</td>
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Quantitative DTI Metrics in a Canine Model of Krabbe Disease: Comparisons vs. Age-Matched Controls Across Multiple Ages

Jonathan Y. Li, Dana M. Middleton, Steven Chen, Leonard White, Charles Vite, Allison Bradbury, James M. Provenzale

*National Institutes of Health, BioMarin Pharmaceuticals, The Legacy of Angels Foundation*

**Background:** The purpose of this study was to compare quantitative DTI metrics in canines affected with a model of Krabbe disease to age-matched normal controls. We hypothesized that fractional anisotropy (FA) would be decreased and radial diffusivity (RD) would be increased in the Krabbe dogs.

**Methods:** Using a highly reproducible region-of-interest (ROI) interrogation technique, FA and RD were measured in three different white matter regions within the internal capsule and centrum semiovale in four Krabbe affected brains and three normal control brains comprising three age-matched pairs.

**Results:** In the young Krabbe dogs, unexpectedly FA values increased and RD values decreased with increasing age in all regions from ages 9 weeks until 14 weeks. In fact, FA values were generally higher and RD values generally lower in both regions of the internal capsule in the Krabbe brains during this period. Thereafter, FA values in the older Krabbe brains decreased and were lower than in control brains and RD values increased and were higher than in control brains.

**Conclusion:** Our findings suggest that FA and RD are affected differently at different time stages in the progression of Krabbe disease. In the young Krabbe brain, higher FA values and lower RD values are seen, which may represent an inflammatory component in the early stages of the disease. However, in the mature Krabbe brain, lower FA and higher RD values are seen, suggesting that the canine Krabbe model may adequately reflect the disease as seen in humans.
Evaluation of colorimetry and biomechanical properties in wounds of dermatologic patients with postoperative infection

Jesse Liu

**Background:** Post-operative infection is rare after dermatologic excisions but is a common concern for patients. Diagnosis of post-operative infection based on clinical presentation alone can sometimes be challenging. Patients unfamiliar with the normal healing process may sometimes confuse normal postoperative changes of the wound such as darkening or itch with infection.

**Methods:** The purpose of this study was to objectively evaluate the appearance of infected and non-infected wounds in Caucasian subjects receiving excisions of non-melanoma skin cancers. We used a colorimeter (Minolta Chromameter) to measure wound color and a biomechanical tissue characterization device (BTC-2000) to determine stiffness. 11 subjects of average age 61.2 ± 10.7 years were recruited for this single-site study. Patients with prior antibiotic use or site infection were excluded. Data were collected pre-operatively and on postoperative day (POD) 14.

**Results:** The most common site was the upper extremity (4/11). 3 patients developed infection, all with Staphylococcus aureus. Colorimetry data are reported in CIELAB color space, which includes light vs dark (L*), magenta vs green (a*), and yellow vs blue (b*). Between POD 0 and 14, average colorimetry changes among all patients were -5.51, 1.27, -2.33, indicating darkening, and gain in magenta and blue hues, respectively. The average colorimetry changes were -3.67, -0.01, and -0.46 in infected patients, and -7.02, 1.89, and -3.96 in uninfected patients. These data suggest that uninfected wounds are actually more likely to be darker and have more magenta and blue hues, but these differences lack statistical significance and are limited by sample size. The average stiffness measurement among all patients was 79.87 ± 33.28 mmHg/mm. Between POD 0 and 14, stiffness increased by an average of 26.73 mmHg/mm. The average stiffness increase among patients with infection was 22.93 mmHg/mm, compared to 28.63 mmHg/mm in uninfected, with no statistically significant difference. Our measurements suggest that wound infection is not necessarily associated with observable changes in tissue color or stiffness. However, 2 of the 3 infected patients reported pus and drainage, and 1 reported significant pain, which may be a more reliable indicator of wound infection than appearance alone.

**Conclusions:** Post-operative infection is rare after dermatologic excisions, but are a common concern for patients. Objective measurements of skin color and stiffness reveal that the appearance and stiffness of the wound may not be reliable indicators of infection. Rather, symptoms such as drainage, pus, or pain may be more suggestive of infection.
Hypoxia inducible factor 1 alpha orchestrates resistance to the novel MAPK/ERK inhibitor SCH772984 by upregulating ABCG2 in a cyclin-dependent kinase 8/19-dependent fashion

Colin A. Martz, Daniel P. Nussbaum, Merve Cakir, Sherry Yang, Lucie Ahn, Emanuel Petricoin, Mariaelena Pierobon, Kevin H. Lin, Kris C. Wood
Poindexter Scholars in Basic Sciences Award

Background: Mutational activation of RAS genes disrupts a carefully regulated endogenous system and yields constitutive signaling that promotes cellular growth and division. RAS gene family alterations are common in diverse cancers and reach a prevalence of over 90% among notoriously lethal pancreatic ductal adenocarcinomas (PDACs). This has stimulated enormous efforts to inhibit RAS therapeutically. While there has been little success in interfering with RAS itself, strategies involving inhibition of its downstream effectors such as the mitogen-activated protein kinase (MAPK) pathway have shown promise. Unfortunately, the tumor-suppressive effects of these approaches are frequently transient owing to an array of resistance mechanisms including epigenetic and transcriptional adaptations.

Methods: In this study, we examined the hypothesis that co-inhibition of various epigenetic and transcriptional regulatory processes alongside MAPK pathway inhibition might delay or preclude resistance to MAPK inhibition in cell-based assays. A pharmacologic screen involving combinations of these agents identified several novel targets that blocked resistance as assessed by growth rate. RNA-sequencing and phosphoprotein array experiments using samples taken over time as resistance developed (or failed to do so) allowed for dissection of the process of adaptive resistance. CRISPR-mediated gene disruption assays were then used to validate putative mediators of resistance.

Results: Inhibition of the paralogous cyclin-dependent kinases 8 and 19 delayed or precluded entirely the resistance to the novel MAPK pathway inhibitor SCH772984 in KRAS mutant PDAC and lung adenocarcinoma cell lines. Resistance to SCH772984 was found to be mediated by upregulation of the efflux transporter ATP-binding cassette subfamily G member 2 (ABCG2). Inhibition of CDK8/19 interferes with the upregulation of ABCG2. The transcription factor hypoxia inducible factor 1 alpha (HIF1a) upregulates ABCG2 in a CDK8/19-dependent fashion. Knockout of either ABCG2 or HIF1a resensitizes SCH772984-resistant cells to the action of the drug.

Conclusions: This study emphasizes the utility of long-term in-vitro assays for credentialing the efficacy of combinatorial cancer therapies. In the specific case of the MAPK pathway inhibitor SCH772984, it outlines a novel mechanism of resistance involving the inducible expression of the ABCG2 efflux transporter that had not previously been demonstrated to act upon this compound. This combination therapy should encourage further efforts to target the transcriptional and epigenetic regulatory responses of malignant cells to targeted therapies in order to impede resistance and improve the efficacy of these agents in the treatment of cancer.
**Project CALM: Confusion Avoidance Led by Music**  
**A Quality Improvement Initiative to Reduce Postoperative Delirium**

Emily Mattoon BS, Neema Sharda MD, Loretta Matters RN, MSN, Judy Prewitt BS, MSN, Shelley McDonald DO, PhD, Richard Sloane MPH, Christy Cassas RN, MSN, FNP-C, Heidi White MD, MHS, Med  
*Duke Institute for Health Innovations and the Maddox Fellowship*

**Background:** Post-surgical older adults are at significant risk for developing delirium, which can lead to higher healthcare costs and worse clinical outcomes. Known risk factors include pain, anxiety, medications, depressed mood, limited mobility & dementia. A meta-analysis of >70 randomized controlled trials strongly supports the use of music post-operatively to reduce pain & anxiety. Personalized music has also been shown to improve challenging dementia related behaviors. Our aim is to operationalize a personalized music program at Duke University Hospital to more effectively manage pain and anxiety thereby improving patients’ experience and decreasing incident delirium (an important quality indicator).

**Methods:** This quality improvement project was implemented on 4 nursing units at Duke University Hospital. Participants were individuals aged 65 or older who were seen in the Perioperative Optimization of Senior Health clinic at Duke University Hospital. These medically complex patients underwent elective surgery requiring at least 1 night inpatient stay (n= 45). The intervention consisted of a post-operative, inpatient personalized music program. Diagnosis of delirium, length of stay and discharge disposition in addition to post-intervention survey responses regarding perceived influence on pain and mood were used as outcome measures.

**Results:** Participants in the personalized music program had a lower rate of delirium (17.8%) compared to an historical group of similar patients (28.7%), despite higher rates of cognitive impairment (81.8% vs 67.5%), a known risk factor for delirium. There was no difference between the groups with regards to length of stay or discharge disposition. Of the patients surveyed after participating in the program, 81% reported a positive effect on their mood and 61.3% reported a moderate or major effect on pain. Additionally, 97.4% reported that they were satisfied or very satisfied with their experience and 89.5% reported that they were likely to continue listening to music at home as a part of their recovery.

**Conclusions:** With successful implementation of an inpatient personalized music program amongst medically complex older adults undergoing elective surgery, we observed decreased rates of postoperative delirium. Most patients reported decreased pain and improved mood regardless of underlying mood disorders, cognitive impairment or hearing deficits. These findings suggest that a personalized music intervention should be embedded more widely as a standard intervention in the postoperative care of adults. Future directions include evaluation of the implementation and impact that music interventions have on clinical outcomes, value measures, and cost to further support the translation of this research endorsed intervention into common practice.
DTI Tensor Shape Analysis for Assessment of Regional White Matter Differences

Dana Middleton, Jonathan Li, Hui Joong Lee, Steven Chen, Patricia Dickson, Matthew Ellinwood, Leonard White, James Provenzale

Background: We set out to investigate a novel tensor shape plot analysis technique of DTI data as a means to assess microstructural differences in brain tissue, and to describe how to create a tensor shape plot from raw DTI data. We hypothesized this technique could distinguish white matter regions with different microstructural compositions. Previous groups have shown that differences in tensor shape metrics can be used to distinguish between cohorts, but none have used differences in tensor shape plots to aid in this distinction.

Methods: Three normal canines were euthanized at 7 weeks of age. The brains were removed and placed in a 10% formalin solution, and imaged using identical DTI protocols on a 7T small-animal MRI. We examined four white matter regions: anterior and posterior regions of the internal capsule (AIC and PIC, respectively) and anterior and posterior regions of the centrum semiovale (ACS and PCS, respectively). We placed 100 regions of interest in each of the four brain regions. Eigenvalues were measured for each ROI. Eigenvalues were used to calculate the shape metrics CS, CL, and CP, which were triangulated onto tensor shape plots as a weighted average of the three shape metrics at the plot’s vertices.

Results: The distribution of data on the plots for the internal capsule differed markedly from the distribution of data on the plots for the centrum semiovale, thus confirming our hypothesis. Furthermore, data for both regions of the internal capsule were distributed in relatively tight clusters, possibly reflecting the compact and parallel nature of its fibers, while data for both regions of the centrum semiovale were more widely distributed, consistent with the less compact and often crossing pattern of its fibers. This finding indicates that the tensor shape plot technique can depict data in similar white matter regions as being alike.

Conclusions: Tensor shape plots successfully depicted differences in tissue microstructure and reflected the microstructure of individual white matter regions. This proof of principle study suggests that if our findings are reproduced in larger samples that include abnormal white matter states, this technique may be useful in assessment of white matter diseases.
Patients with Breast Cancer Brain Metastases Demonstrate an Improved Overall Survival over the Past Two Decades

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Background: Breast cancer brain metastasis (BCBM) is a serious complication in advanced breast cancer and associated with poor prognosis. Optimized treatments and diagnostics have improved overall survival in metastatic breast cancer. It remains unclear whether these therapeutic advances have impacted the survival of patients with BCBM.

Objective: To analyze trends in survival for patients with BCBM over the past two decades and correlate findings with other clinicopathologic variables.

Methods: This is a single institution retrospective review of patients diagnosed with BCBM between 1996-2015. Data collection includes: age, ethnicity, hormone receptor (HR) status, HER2 status, date of brain metastasis diagnosis, date of primary cancer diagnosis, date of death, and treatment regimens after BM diagnosis. OS (from BCBM until death) was plotted using Kaplan-Meier methods. Log-rank tests compared the survival distribution of two or more groups. A multivariate proportional hazards model was used to regress overall survival on date of BCBM diagnosis adjusted for clinicopathologic and treatment variables.

Results: A total of 250 patients with BCBM were included, with a mean age of 53.6 at time of BCBM diagnosis. Primary breast cancer subtype analysis showed 36% HR+/HER2-, 31% HR-/HER2-, 18% HR+/HER2+, and 15% HR-/HER2+. Few patients (12%) received surgical resection of BCBM, and 67% received systemic treatment after BCBM diagnosis. Most patients (83%) received brain radiation (WBRT alone - 59%, SRS alone - 12%, WBRT & SRS – 12%). Median overall survival improved for patients diagnosed with BCBM between 2006-2015 as compared to patients diagnosed between 1996-2005 (8.9 vs 5.4 months), p=0.048. Median OS differed by prognostic subtypes: HER2+ 18.1 months; HR+/HER2- 6.5 months; HR-/HER2- 4.4 months, p<0.001. Tumor status, breast cancer subtype, and all post-BCBM treatment modalities were significantly associated with improved overall survival in univariate models.

Conclusions: Median overall survival has improved by 3.5 months over the past two decades and is highly dependent upon HER2 status and post-BCBM systemic therapies. These findings lend support for continued use of molecularly targeted therapeutics and development of novel systemic treatment strategies in patients with BCBM.
Utility of Staging PET-CT in Patients with Melanoma and a Positive Sentinel Lymph Node Biopsy

Neel Nath, Gabriel Li, Visakha Suresh, Adam K. Brys, April K.S. Salama, Brandon A. Howard, Paul J. Mosca

Background: Patients with melanoma who have clinical or pathologic nodal disease are typically evaluated for distant metastases using cross-sectional imaging. In the subset of stage III patients who have a newly diagnosed primary melanoma with clinically occult nodal disease in the form of a positive sentinel node biopsy (SLNB), previous studies have found a low frequency of detectable metastases with cross-sectional imaging. Fluorodeoxyglucose (FDG) positron emission tomography in combination with computed tomography (PET-CT) has gained acceptance as an imaging modality of choice for identifying metastatic melanoma. The aim of this study was to evaluate the utility of PET-CT in staging patients with melanoma who have a positive SLNB.

Methods: A single-center, retrospective review was performed of all patients seen at Duke University Medical Center who were imaged with PET-CT from January 1, 2005 to October 7, 2016 for a diagnosis of melanoma.

Results: Of the 84 patients with positive SLNB, clinically occult nodal involvement, and a PET-CT scan within 3 months of their initial diagnosis, PET-CT detected distant metastasis in only 1 patient (1.2%). This patient had a primary melanoma with a Breslow thickness of 11 mm.

Conclusions: These findings indicate that staging with PET-CT in patients with melanoma on the basis of positive SLNB rarely provides information that is likely to change management. Further study is warranted to determine what factors would most reliably predict which of these patients who are likely to benefit from baseline staging PET/CT.
Quality of Hospital Management is Associated with Neonatal Outcomes in India

Stephanie Pagliuca, Raffaella Sadun, Sofi Bergkvist, Kedar Mate, Ajitkumar Sudke, Alex Haynes

**Background:** Many healthcare organizations fail to implement known safety practices, despite evidence of their effectiveness, even in the context of overt commitment to change programs. One explanation for this is variation in management. A recent initiative involving the World Management Survey indicates that there is significant variation in the quality of hospital management practices, not only within and across countries, but also across hospital systems and even departments at individual institutions. Further, this variation has been linked to quality of clinical care. We sought to investigate whether the managerial capabilities of clinical leads play a role in shaping the safety culture of an organization, the adoption of safety practices and, ultimately, patient outcomes.

**Methods:** We assessed management practices and safety culture in 23 hospitals in India taking part in a neonatal care improvement program. Using the World Management Survey, we quantified the adoption of basic management practices across four domains - Operations, Monitoring, Target Management, and People Management. We then matched this with degree of intervention uptake, perceived safety culture, and neonatal mortality rates.

**Results:** We found that hospitals with management scores in the upper tercile had better safety culture, safety practice adoption, and neonatal mortality rates (all $p<0.05$). This difference remained significant even when controlling for NICU admissions, total number of hospital beds, and hospital state (Andhra Pradesh or Telangana).

**Conclusions:** Our results support the hypothesis that the ability to execute on clinical quality improvement initiatives—and their effect on clinical outcomes—may be mediated by both management and safety culture. Attention to the basic management capabilities of clinical leads may facilitate effectiveness of improvement initiatives.
Alterations in hippocampal subfield volume in collegiate athletes participating in high-contact sports: A 5-year longitudinal study

Sherveen Parivash, Maged Goubran, Paymon Rezaii, Wei Bian, Brian Boldt, Huy Do, David Douglas, Eugene Wilson, Lex Mitchell, Mansi Parekh, Scott Anderson, Gerald Grant, Michael Zeineh

RSNA Medical Student Research Grant

Background: Emerging research suggests that mild traumatic brain injury (mTBI) may lead to long-term neurological abnormalities, with evidence suggesting that such injury is associated with deficits in memory and reduced hippocampal volume. Contact sports athletes, in particular, are at increased risk for TBI, with cross-sectional MR imaging studies demonstrating that repeated concussive and sub-concussive injury in collegiate football players is correlated with significantly lower hippocampal volumes compared to healthy controls. Here we report the longitudinal effects of mTBI on hippocampal subfield volume in contact sports athletes.

Methods: A total of 297 MRI scans from 63 high-contact (football) and 34 age-matched, low-contact (volleyball) players over the course of 5 years, in accordance with IRB and HIPAA data collection and storage procedures. For each subject, hippocampal segmentation was achieved using Automated Segmentation of Hippocampal Subfields, which employs T1 and T2-weighted MR images alongside an atlas to obtain reliable segmentation of the hippocampal subfields and medial temporal lobe cortices. We employed a linear mixed model with random effects to interrogate differences in regional hippocampal subfield volume, with temporal correlations for each subject with repeated measures. Multiple comparison correction was performed using false discovery rate (FDR) with an alpha of 0.05 for each hippocampal subfield.

Results: We found that, after FDR correction, the RA-CA1 hippocampal subfield (p=0.025) volume was significantly smaller in high-contact compared to low-contact athletes. Average RA-CA1 hippocampal volume decreased over time in high-contact athletes, while average hippocampal volume increased in low-contact athletes over time. Whole hippocampal analysis for both sides were not found to be significant, although the whole right hippocampus showed a similar trend (p=0.067). There were no significant differences in whole hippocampal or subfield volume between groups at baseline.

Conclusions: Using hippocampal volumetry, we show differences in subfield volumes between high and low-contact collegiate athletes in this longitudinal analysis. We show that, on average, anterior hippocampal volumes appear to be trending down over time for high contact sports athletes, potentially as a result of repeated mTBI, though any mechanisms for this change remain unknown. On hippocampal subfield analysis, we find significant longitudinal differences between groups, suggesting that a relationship exists between repeated mTBI and hippocampal subfield volume.
Neuropeptides and Scleroderma

James Parra, Dr. Mary Sunday M.D. Ph.D.

**Background:** In previous studies, gastrin-releasing peptide (GRP) has been shown to play a role in pulmonary fibrosis and the development of that fibrosis could be abrogated via GRP blockade. As a logical extension of this finding, this study aims the hypothesis that ROS mediated GRP release contributes to fibrosis in a murine bleomycin model of scleroderma.

**Methods:** Mice were separated into groups, all receiving intradermal bleomycin to induce oxidative stress and fibrosis. Groups were then additionally either treated with N-acetylcysteine (a potent antioxidant), an anti-GRP monoclonal antibody, or PBS (control). Results were assessed using Masson’s trichrome and IHC for relevant markers of fibrosis.

**Results:** Micropictographs were taken and analyzed using ImageJ. The study showed a significant decrease in dermal thickness between the control group and both the GRP blockade and NAC treated groups (P<0.0001), thus supporting our hypothesis.

**Conclusions:** Reactive oxygen species mediated oxidative damage plays a role in fibrotic skin change in scleroderma. Elimination of oxidative stress via administration of NAC and GRP blockade show reduction in fibrotic changes in bleomycin treated murine skin.
A Retrospective Descriptive Study of Patients Treated in the Durham Veterans Affairs Leg Ulcer Clinic, an Equal Access Setting

Michael Peterson, Lionel Banez M.D., Caroline Rao M.D., Adela Rambi G. Cardones M.D.

**Background:** Chronic leg ulcers affect a large number of patients over 60 and cause significant morbidity to patients and financial burden to the health care system and society. We set out to study a population of leg ulcer patients seen in the equal access setting of the Durham Veterans Affairs leg ulcer clinic by describing the demographics, comorbidities, disease characteristics, and outcomes while identifying factors that may influence outcomes in this population.

**Methods:** A retrospective chart review of patients seen in the Durham Veterans Administration (DVA) leg ulcer clinic was conducted and population characteristics and outcomes were assessed. This data was then analyzed and to produce descriptive statistics about this population as well as to identify associations between variables and patient outcomes.

**Results:** This is a predominantly male (96.4%) population with mean age of 56.56 years. Common health risk factors and comorbidities include obesity (75.3% of patients had BMI >30), tobacco use (63.6% current or former smokers), thromboembolic/vasooclusive disease (31.6%), congestive heart failure (28%), foot ulcer (28.4%), coronary artery disease (25.8%), peripheral arterial disease (24%), diabetes mellitus (46.4% had Hgb A1c > 6.5) hypoalbuminemia (55.2%), elevated creatinine (48%).

**Conclusions:** Preliminary statistics show statistically significant associations with mortality including: older age, lower BMI, greater pack year smoking history, elevated serum creatinine, decreased serum albumin, history of congestive heart failure, myocardial infarction, thromboembolic disease, taking aspirin, and receiving home health services. Further statistics are needed to correct for confounding variables and establish independent association.
Trends in Opioid Utilization Before and After Total Knee Arthroplasty

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Background: Opioids are a mainstay in perioperative pain management among patients who undergo total knee arthroplasty (TKA). However, opioid use before and after TKA has not been well-studied. The objective of this study was to characterize prescribing trends pre- and postoperatively and to identify risk factors for chronic opioid use.

Methods: A review of the prescription-tracking database of a large private payer from 2007 to 2013 was performed using ICD-9 and CPT codes. Chronic opioid use was defined as opioid prescriptions over six contiguous months postoperatively.

Results: We identified 66,950 patients who underwent TKA with a minimum follow-up of two years and medication codes. 36,668 (54.8%) patients were prescribed opioids within one year preoperatively (opioid cohort), and 30,282 (45.2%) patients were opioid-naïve preoperatively. 34.8% of the opioid cohort became chronic users postoperatively compared to 5.0% of the opioid-naïve cohort (OR, 10.144; CI, 9.592-10.728). Females had higher odds than males of chronic use post-TKA (OR, 1.655; CI, 1.567-1.749), and patients 40-59 years old had higher odds of chronic use than over-59-year-olds (OR, 3.504; CI, 3.197-3.840). From 2007-2013, tramadol and oxycodone use increased linearly preoperatively (R-square = 0.9372; R-square = 0.6177, respectively) and postoperatively (R-square = 0.9907; R-square = 0.8684, respectively), but chronic opioid use post-TKA did not increase.

Conclusions: The greatest risk factors for chronic postoperative opioid use were opioid use pre-TKA, younger age, female gender, greater LOS, and CCI. While the increased use of certain opioid classes continues to grow perioperatively, the rate of chronic opioid use post-TKA has not changed over time.
Investigation of mechanisms of thermal ablation zone enlargement when combined with transarterial embolization for treatment of liver tumors

Charles Puza, Charles Kim MD
RSNA Medical Student Grant, SIR Culp Student Grant

Background: Percutaneous thermal ablation has evolved into a first-line interventional therapy for hepatocellular carcinoma (HCC). In fact, it is recommended by NCCN as the favored treatment for liver tumors of 3-5 cm. While thermal ablation has evolved into a commonly used curative modality for treatment of HCC, its efficacy is limited by tumor size. The recurrence-free survival rate is significantly better with smaller tumor sizes. Embolotherapies (TACE and TAE) have long been a vital and common treatment option for patients with HCC, having been shown to have a survival advantage over best medical management. However, these various embolotherapies are very rarely curative, with a substantial recurrence rate. While both embolization and thermal ablation therapy for liver tumors have been proven to be effective, the combination of these two therapies has been shown to result in improved responses. In fact, TACE combined with RFA has been shown to increase the size of ablation zone compared to RFA treatment alone, creating tumor free margins more often ((74.0-83.3 vs. 22.2 %, p < 0.05). Additionally, survival is improved with combination therapy combined to monotherapy (32.8 months compared to 21.3 months, p=0.0035).

There are two competing theories as to why combination embolotherapy with RFA increases the zone of ablation. It is understood that TAE induces ischemia in target tissues. The ischemia is believed to augment the cell death caused by RFA. The other competing theory, known as the “heat sink” theory, postulates that by stopping the arterial blood flow, and heat cannot be carried away from the site of RFA. As more heat is focuses at the site of RFA, a hotter temperature is reached and thus more tissue can be ablated.

While there are a number of potential mechanisms for this benefit, the exact factors and relative degrees of contribution of benefit are not understood. Although this combination approach has been proven effective, there is an incomplete understanding of the actual mechanism of enhanced efficacy. The goal of this project was to investigate the underlying mechanism of this response.

Methods: HepG2 cells were cultured, exposed to 1%, 5%, and 20% hypoxia conditions, incubated for 10 minutes at either room temperature, -80° C, -20° C, 50° C, 60 °C, or 70° C, then assessed for viability. In vivo studies were performed with rabbits, embolized with nothing, embozene, or iron oxide, and then separated into control, radiofrequency ablation, or microwave frequency ablation groups.

Results: Increasing degrees of hypoxia resulted in lower threshold and greater percentage of cell death compared to controls. Embolization does not significantly allow for higher temperatures in liver ablation zones.

Conclusions: Hypoxia significantly contributes to the enlargement of the ablation zone in combination embolization and ablation of liver tumors.
Enhancing Employee Empowerment by Celebrating the Red Dots

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Background: Empowerment and engagement of frontline employees in continuous improvement is an essential component of a healthy organizational culture. Previous studies have evaluated the utility and effectiveness of employee suggestion programs regarding its ability to improve worker empowerment and shared decision-making. We hypothesized that implementing a collaborative improvement system in which the submission of ideas is actively encouraged and acknowledged would improve staff engagement and work culture. The aim of this pilot study was to evaluate the feasibility, utility, and perceptions of a modified employee suggestion program on one inpatient hospital ward.

Methods: The pilot study was conducted over the course of 12 weeks in a 32-bed General Surgery Patient Care Unit of Duke University Hospital. Staff was encouraged to submit non-time sensitive problematic issues encountered during the daily workflow, referred to as “red dots.” An inter-professional committee comprised of personnel from the unit met weekly to evaluate submissions to determine red dot categorization and priority prior to discussing how they might be resolved. Additionally, annual work culture survey scores from 2014 through 2016 were examined for changes consistent with an impact on local culture.

Results: At the end of the pilot, a total of 64 submissions were received. Of the 64 submissions, 14 (22%) were resolved, 28 (44%) ongoing, 13 (20%) are progressing, and nine (14%) had not been started. Of the 14 resolved red dots, 7 (50%) were resolved within 0-2 days following their submission; nine of which were first acted upon within 0-3 days following their submission. The majority of red dots noted arose from areas of quality of care (32), patient safety (37), and staff comfort (21). Among the six prospectively selected survey items, there was a significant increase in work culture performance scores as compared to two years and one-year prior. Notably, work culture performance score for question ‘my ideas and suggestions are seriously considered’, increased from 3.38 in 2015 to 4.05 in 2016. The score for question, ‘I am involved in decisions that affect my work’ increased from 3.19 in 2015 to 3.82 in 2016. Lastly, the work culture performance score for question 25 ‘my entity makes every effort to deliver safe, error-free care to patients’ increased from 3.56 in 2015 to 4.29 in 2016. From 2015 to 2016 the hospital unit overall work culture performance increased from Tier III to Tier II demonstrating improved workforce engagement.

Conclusions: This study describes an approach to continuous improvement on a General Surgery Patient Care Unit focusing on employee engagement and empowerment with potentially positive effects on work culture. The findings of this study provide evidence for the feasibility and ease of use of an employee suggestion program to be incorporated within a hospital unit. While a larger and more rigorous study is needed to draw definitive conclusions regarding the broader impact of this system, the empowerment of frontline workers using a Kaizen-inspired system may have important implications for improved workplace culture, engagement, and productivity in healthcare.
Knowledge and Perceptions Regarding Palliative Care among Religious Leaders in Uasin Gishu County: Survey and Focus Group Analysis

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Doris Duke International Clinical Research Fellowship

Background: Addressing spiritual and religious concerns are key components in providing palliative care (PC) to patients with chronic and life-threatening illnesses in Kenya. Involvement of religious leaders is crucial to strengthen already broad advocacy and education efforts underway in Kenya. Therefore, better understanding what the religious leaders know and think about PC is important. The overall goal of this study was to evaluate the knowledge and perceptions of religious leaders in western Kenya regarding PC. We had three objectives.

Methods: This was a mixed-methods study that utilized a 25-question survey followed by 5-person focus group discussions (FGD) with a total of 86 religious leaders. Informed consent for participants was obtained followed by completion of the paper survey and then FGDs. Survey data were analyzed in Excel® for univariate and bivariate measures. To compare responses based on training and religious affiliation, Chi square testing was used on ordinal responses which were collapsed to nominate levels of agree vs disagree. Audio data from the focus groups were transcribed and translated to English. NVIVO software was then used for text analysis and coding to identify important themes.

Results: 80% of the participants were male and 71% were between the ages of 30 and 50. 74% held either an advanced diploma or theology degree. 47% led churches of less than 100 members while 36% and 16% represented churches of 100-300 or greater than 300 respectively. 37% of the participants strongly agreed that talking with patients with incurable illness about end of life care was beneficial but 31% either disagreed or strongly disagreed. Only 29% believed that full use of palliative care principles would hasten the death of their church members. Slightly more than half (68%) the participants reported a good understanding of palliative care. There was broad sentiment supporting spiritual/pastoral care as a routine part of inpatient care and the need for better home based care for church members. Chi square testing showed ethnicity had an impact on the perception of talking about death. The main themes emerging from the FGDs confirmed the important roles of religious leaders, teamwork and collaboration. The pastors underscored challenges in end of life preparation and importance of traditions and cultural norms surrounding end of life. They supported the need for community based PC education and future training of religious leaders in PC.

Conclusions: The results from this study support the need for continued palliative care advocacy efforts in the pastoral community. They are key stakeholders in end of life care in Kenya. Better training for pastoral leaders should foster more widespread adoption of PC principles while respecting traditional beliefs and cultural norms surrounding death and dying in Kenya.
Understanding the contribution of CX3CR1⁺ myeloid cell-specific TNF-α in mediating hypertensive end organ damage

Justin Rucker
Eugene A. Stead Scholarship

**Background:** Hypertension afflicts more than 1 billion people worldwide and is a leading risk factor in the development of myocardial infarction, stroke, and chronic kidney disease. Despite this, much of the pathogenesis of essential hypertension remains poorly understood, hindering the development of more efficacious therapies to control blood pressure. The study of immune cells and their canonical pro-inflammatory cytokine, tumor necrosis factor alpha (TNF-α), has provided key insights into immunomodulatory mechanisms responsible for inducing hypertension and subsequent target organ damage. Our lab has previously demonstrated that selective depletion of TNF from the kidney can attenuate end-organ injury in response to hypertension. However, it remains unclear which cell lineage is the source of the TNF responsible for mediating these effects. As there is a dense network of resident kidney myeloid cells expressing the chemokine receptor, CX3CR1, we posited that these cells were a promising candidate for the renal source of TNF involved in the hypertensive response. As kidney fibrosis can result from long-standing hypertension, we hypothesized that selective deficiency of TNF in CX3CR1 expressing cells would attenuate kidney injury and fibrosis.

**Methods:** To test the contribution of TNF generated by resident kidney myeloid cells to renal fibrosis, we generated mice with specific deficiency of TNF in CX3CR1⁺ cells (CX3CR1⁻Tnf⁻/⁻) and subjected these animals along with their control, Tnf⁺/⁺, littermates to the unilateral ureteral obstruction (UUO) model of kidney fibrosis. Kidney injury and fibrosis was quantified in the obstructed kidney using real time RT-PCR to measure mRNA expression of TNF-α, Collagen 1, PAI-1, NGAL, TGF-β, IL-1β, and Fibronectin. These were then compared to the mRNA expression of these genes in the contralateral, uninjured kidney to validate the efficacy of our assay. Prior to this experiment, we verified specific deletion of TNF in CX3CR1⁺ cells by measuring expression of TNF from sorted CX3CR1 + and CX3CR1⁻ cells as well as heart and kidney tissues. Additionally, confirmation of myeloid cell markers in renal CX3CR1⁺ cells was performed using flow cytometry.

**Results:** Our initial studies indicated a substantial reduction in both mRNA (0.0113 ± 0.0022 versus 1± 0.081 arbitrary units [a.u.]; p < 0.0001) and protein (30.1% versus 98.8%; p < 0.0001) expression of TNF-α in CX3CR1⁺ cells harvested from our CX3CR1⁻Tnf⁻/⁻ mice compared to Tnf⁺/⁺ controls. Further, CX3CR1⁻Tnf⁻/⁻ mice also had drastically diminished renal TNF mRNA expression (0.28 ± 0.032 versus 1± 0.15 a.u.; p < 0.0001). Despite these contrasts at baseline, we found no difference in markers of fibrosis and inflammation after 7 day UUO between our CX3CR1⁻Tnf⁻/⁻ and control mice (n=12 and 11). Specifically, levels of TNF mRNA were similar in the control and CX3CR1⁻Tnf⁻/⁻ kidneys at day 7 after UUO.

**Conclusions:** We conclude that CX3CR1⁺ cells are a major source of TNF in the kidney under normal, homeostatic conditions, but that another cell lineage produces the TNF responsible for mediating renal injury in UUO.
Effects of Dextromethorphan in a SUDEP mouse model

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Background: There exists a gap in knowledge of medications that could prevent sudden unexpected death in epilepsy (SUDEP). Recent data suggests that SUDEP is related to spreading depression (SD), a self-propagating wave of depolarization in the cerebral cortex. Our Mashl+/− model of Alternating Hemiplegia of Childhood (AHC) shows increased predisposition to SD and SUDEP. SD has been shown to be propagated by NMDA receptor activation, and dextromethorphan (DXM), which has anti-NMDA blocking properties, has been shown to attenuate SD. Thus, our aim was to study DXM’s effects on SD and SUDEP in our animal model.

Methods: We compared the frequency of SUDEP during 4 quarters of life in the Mashl+/− model. 4 groups were studied to observe the in vivo effects of DXM. 2 groups of WT and 2 groups of Mashl+/− mice, one of each receiving vehicle and one of each receiving DXM (20 mg/kg). Animals underwent vestibular stimulation once/day for 10 days 20 minutes after receiving vehicle/DXM. Then animals were subjected to flurothyl-induced seizures. To examine DXM’s effects in vitro, brain slices from WT and Mashl+/− animals were subjected to spreading depression in the CA1 hippocampal region using high concentrations of KCl, and treated with various concentrations of DXM.

Results: Mortality was significantly higher in the second quarter of life of Mashl+/− mice: n = 39, P < 0.05, x² test (7/39 in the 1st quarter; 16/39 in the 2nd; 11/39 in the 3rd; and 5/39 in the 4th) over a 24 month period. During this period, 10 Mashl+/− mice were directly observed to have spontaneous seizures with 40% (4/10) undergoing SUDEP immediately following the seizure. After undergoing vestibular stimulation, all Mashl+/− mice had seizures irrespective of whether they received DXM or vehicle. Preliminary results showed a trend that DXM treatment decreases seizure latency in both WT and Mashl+/− mice (WT, n = 2, P = 0.058; Mashl+/−, n = 2, P = 0.052). Spreading depression duration was significantly inhibited at high concentrations of DXM in WT animal brain slices (P = 0.050); however, no such effect was observed in Mashl+/− slices. Spreading depression amplitude remained unaffected in both WT and Mashl+/− slices.

Conclusions: SUDEP occurred most commonly during the second quarter of life and by virtue of the occurrence of stimulus induced seizures this model can be used as model to screen for potential anti-SUDEP medications. DXM offered no protection against death and SD in vivo. Unlike previous studies in adult mice, we did not find any protective effect of DXM in vitro.
Keeping Care Connected: E-Consultation Program Improves Access to Nephrology Care


Duke Institute for Health Innovation (DIHI) Clinical Research and Innovation Scholarship

Background: As access to specialists becomes increasingly difficult for patients and primary care providers (PCPs), health systems are seeking innovative solutions to improve specialty care access. Electronic consultations (eConsults) allow specialists to provide formal clinical recommendations to PCPs based on patient chart review, without a face-to-face visit. E-Consults may be an effective strategy to improve patient access to specialty care and enhance the primary care to specialty care interface.

Methods: We implemented a Nephrology eConsult pilot program within four Duke Primary Care clinics to facilitate timely communication between nephrologists and PCPs. We used primary care referral data to compare wait times and completion rates between traditional referrals placed in Fiscal Year 2016 (from July 1, 2015 to June 30, 2016) and eConsults. We surveyed PCPs to assess their satisfaction with the program.

Results: At baseline for traditional referrals, there was a 61-day median appointment wait time and a 30.8% referral completion rate for nephrology referrals. For eConsults, there was a median nephrologist response time of one day and a 100% completion rate; 67.5% of eConsults did not require a subsequent face-to-face specialist appointment. For eConsults that were converted to an in-person visit, the median wait time and completion rate were 40 days and 73.1% (p<0.00001), respectively. Survey responses revealed that PCPs were highly satisfied with the program and consider the quick turnaround time as the greatest benefit.

Conclusions: Our eConsult pilot program improved access to specialist appointments and enabled timely care coordination between primary care and nephrology. Results show reduced nephrology care wait times, significantly increased referral completion rates for patients within our primary care network, and improved closure of the specialty referral loop. In large integrated health systems, eConsults have tremendous potential to improve access to specialty care, reduce unnecessary appointments, and optimize the patient population being seen by specialists.
Prevalence and Clinical Importance of Sarcopenia in Women with Breast Cancer Treated with Antiandrogen Therapy

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National Cancer Institute, AKTIV Against Cancer, Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748)

Background: A small subset of breast cancer patients have tumors which demonstrate androgen receptor (AR) overexpression responsive to androgen blockade therapy. In general, outside the context of breast cancer, reducing bioavailable androgens causes profound changes in body composition including increase in whole-body and visceral fat mass with concomitant loss of lean body mass – a syndrome known as sarcopenic obesity. Importantly, sarcopenia is a strong predictor of treatment toxicity and poor survival in several populations with advanced cancer. Against this background, the purpose of this study was to examine the utility and clinical importance of computed tomography (CT) derived body composition assessments in women with metastatic breast cancer receiving antiandrogen therapy.

Methods: This study was a retrospective analysis of clinical data and imaging parameters in a cohort of patients with histologically confirmed androgen positive metastatic breast cancer. CT-derived images obtained as part of standard of care were used to assess changes in a variety of body composition parameters at the third lumbar spine (L3) including muscle mass (cm$^3$), subcutaneous and visceral fat mass (cm$^3$), psoas muscle composition, and skeletal muscle index (cm$^2$/m$^2$). These measurements were taken before beginning antiandrogen therapy and again at the first follow up clinical assessment with a median interval of 69.5 days (range: 34 – 175 days).

Results: Fifty-two postmenopausal, HER2 negative patients with a median age of 60 years (range: 35-85) were included in the analysis. All were post-menopausal and HER2- with 27 (52%) ER+. Of the 52 patients, 33 (63%) had sarcopenia at baseline. No relationship was found between sarcopenia and OS (median: 25.8 months vs. 25.7 months p=0.46) or POD (median: 3.2 months vs. 2.9 p=0.59). L3 muscle volume was marginally lower at interval scan compared with baseline with a median change of -8 cm$^3$ (p=0.052). There was a trend towards significance for L3 muscle volume with OS (HR: 0.93, 95% CI: 0.87-0.98, p=0.11). Psoas high-density muscle was slightly, but not significantly lower at interval scan with a difference of -0.1 cm$^3$ (p=0.09), as were psoas fat (p=0.09).

Conclusions: This was the first study to evaluate changes in body composition measures in women taking antiandrogen therapy. Our group found variable changes in body composition during treatment with a general trend towards loss in muscle mass and gain in fatty infiltration of muscle reflecting poorer ‘quality’ muscle. We did not find any of these parameters to be predictive of OS or POD, therefore whether these changes in body composition are clinically important remains unknown. As more women are placed on antiandrogen therapy earlier on in their disease and for longer periods of time, it will be important to better characterize the systemic effects of antiandrogen therapy.
An Evaluation of the Effectiveness of the HPV Vaccine in Preventing Genital Warts and Cervical Disease Among Young Women at Duke

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Background: Human Papilloma Virus (HPV) is the most common sexually transmitted infection in the United States and is responsible for nearly all cases of cervical cancer and its pre-cursor lesions. The HPV vaccine, introduced in 2006, has demonstrated dramatic global effectiveness in the prevention of genital warts and HPV-related cervical disease. However, there are currently no data describing the vaccine’s effectiveness among Duke’s patient population.

Methods: A retrospective review of filtered electronic medical record (EMR) data was performed to identify women ages 18-34 years old with HPV-related diagnoses of interest from 2000-2015. The annual overall, age-specific and race-specific incidences of each considered diagnosis were calculated for North Carolina at the state and county level using extracted EMR data and publicly available census data.

Results: The calculated incidences were generally downward trending over the study period across all HPV-related diagnoses for the younger evaluated age groups, while results were less consistent for women ages 25-34 years old. A 2015 increase in the overall incidence of all considered diagnoses except high risk HPV infection was observed and appears to have been driven largely by women 25-34 years old. The annual incidences of all considered diagnoses were consistently higher among African American women than Caucasian women.

Conclusions: While the presented data indicate an encouraging downward trend in most of the considered HPV-related diagnoses after 2006, particularly among younger women, an obvious racial disparity in overall outcomes persists suggesting the need for further research to evaluate potential causes of these disparate racial outcomes and strategies to address them.
Estimation of Achievable Oxygen Consumption Following Transfusion with Rejuvenated Red Blood Cells

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Background: Erythrocyte storage induces a non-physiological increase in hemoglobin-oxygen affinity (quantified by low p50, the oxygen tension at 50% hemoglobin saturation), which can be restored through biochemical rejuvenation. The objective was to mathematically model the impact of transfusing up to three standard allogeneic units or rejuvenated units on oxygen delivery (DO2) and oxygen consumption (VO2).

Methods: Oxygen dissociation curves were generated from AS-1 RBC leukoreduced units (n = 7) before and after rejuvenation following manufacturer’s instructions. Two of these units were used to prepare standard or rejuvenated donor RBC and added to samples of fresh whole blood (WB). These admixtures were used to construct an in vitro transfusion model of post-operative anemia and determine a linear equation for calculating the sample p50, which was subsequently used to calculate DO2 and VO2 after simulated transfusions.

Results: WB/PRBC admixture p50s could be predicted from a linear model including the p50 of its components, the mass fraction of the transfused component, and interaction terms ($R^2 = .99$, $p<0.001$). Transfusion with standard units slightly, but significantly, increased projected DO2 compared to rejuvenated units ($p<0.001$), but rejuvenated units markedly increased projected VO2 ($p<0.001$). Standard units did not significantly change VO2 relative to pre-transfusion levels ($p>0.1$).

Conclusions: Using high-p50, rejuvenated RBC in simulated transfusions greatly improved projected VO2, indicating the potential for increased end-organ oxygen availability compared to standard transfusion. Patient capacity to increase cardiac output after cardiac surgery may be limited. Transfusing high-p50 RBC in this setting may improve the perioperative care of these patients.
Hearing Loss and Healthcare: Experiences of hard-of-hearing patients in a primary care setting

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T32DC013018 Training for Clinical Research in Hearing, Balance and Other Communication Disorders

**Background:** Hearing loss is a highly prevalent sensory deficit that increases with age and interferes with effective communication on a daily basis. People with hearing loss have higher healthcare utilization rates and costs. Miscommunication and unmet needs in the healthcare setting have not been well characterized for older adults with hearing loss.

**Methods:** A survey developed by experts in the field asked respondents to rate the difficulty they experienced understanding various healthcare personnel, as well as their difficulty understanding in a variety of healthcare situations during a recent office visit. A link to the survey that allowed anonymous responses was posted on a website and information about the study along with the link was sent out via email to the listserv of a large national hearing-loss consumer and advocacy group (Hearing Loss Association of America). Data were collected and managed via RedCAP.

**Results:** Responses were received from 1,581 individuals. The majority of respondents utilized amplification devices (>93%). Respondents reported moderate or significant difficulty communicating with all listed providers more than 50% of the time. Three situations resulted in respondents sometimes or often having difficulty understanding: hearing their name called in the waiting room, when the speaker’s back was turned (such as to look at a computer) and when communicating by telephone. Cochlear implant users (OR=10.46) and females (OR=1.98) were more likely to make healthcare providers aware of their hearing loss, but 29.3% of respondents reported that no arrangements were made even after alerting personnel to their needs.

**Conclusions:** This study clearly demonstrates the ongoing difficulties faced by patients with hearing loss as they attempt to navigate both providers and situations associated with a typical primary care office visit. Inexpensive and efficient changes in healthcare delivery are recommended that could dramatically improve patient understanding of health care related communication, experiences, and satisfaction with healthcare services.
Dual Antiplatelet Therapy Utilization and Cardiovascular Outcomes Among Black and White Patients Treated with Drug Eluting Stents: A Retrospective Analysis of the Duke Databank for Cardiovascular Disease

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Background: It is unclear how patterns of dual antiplatelet therapy (DAPT) use following drug eluting stent (DES) implantation vary by race.

Methods: We retrospectively analyzed 4,474 black and white patients who underwent DES placement at Duke University Medical Center from 2005 through 2013. Dual antiplatelet therapy use was compared by race at discharge, 6 months, and annually thereafter. Long-term outcomes including MI, death, revascularization and bleeding were compared by race and duration of DAPT.

Results: Black patients were younger, more likely to be female, and had more diabetes, hypertension, and renal disease than white patients (p<0.001). The majority of black (96.1%) and white (96.6%) patients initiated DAPT at discharge and DAPT use did not differ significantly by race at any point during follow-up. Black race was not predictive of premature discontinuation of DAPT (p=0.81). Blacks in the baseline population had higher unadjusted rates of MI (12.08% vs. 10.11%, p=0.05) and bleeding (17.80% vs. 14.26%, p=0.01) than whites, but the rate of revascularization was similar (23.51% vs. 24.44%, p=0.80). There were no differences in adjusted outcomes by race. Similarly, the adjusted rates of MI, death, revascularization and bleeding did not differ between blacks and whites on standard DAPT irrespective of DAPT duration.

Conclusions: Use of DAPT over time at Duke University Medical Center is comparable between black and white patients. Blacks with DES have worse long-term outcomes than whites and these differences are partly explained by differences in baseline comorbidities and household income.
Dengue virus activates cGAS through the release of mitochondrial DNA (mtDNA)

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Duke-Singapore Student Scholar Fellowship

Background: Dengue fever, a mostly tropical/subtropical mosquito-borne illness, has become a major emerging infectious disease in recent decades, with approximately 300-400 million infections yearly. The disease is caused by dengue virus (DENV), a positive-sense single-stranded RNA virus (+ssRNA) part of the Flaviviridae family. Although a vaccine, Dengvaxia (CYD-TDV), has recently been licensed in many endemic countries such as Singapore and Thailand, its efficacy is most pronounced in and somewhat limited to patients with previous DENV exposure. Therefore, more must be done to develop a dengue vaccine of use to a larger population. Because the most effective vaccine strains activate antiviral interferon signaling in the host, to best design the most effective dengue vaccine, we must develop a comprehensive understanding of the pathways linking DENV infection and interferon production. One pathway of interest involves the cytosolic protein cyclic GMP-AMP synthetase (cGAS), which has recently been identified as important in countering +ssRNA activity. It is paradoxical, however, that cGAS binds specifically to DNA while its activity has been shown to be induced by RNA viruses such as DENV. This project ultimately aims to characterize how cGAS is activated by DENV.

Methods: All experiments were performed in vitro with A549 (human lung carcinoma cells) or BHK21 (baby hamster kidney cells), and cell infections were done with DENV-2 PDK53, a candidate vaccine strain developed at Mahidol University in Thailand and a known strong inducer of interferon signaling. DENV replication and mitochondrial DNA (mtDNA) levels were measured using RT-qPCR. The activity of cGAS was measured by quantifying its enzymatic product, cyclic GMP-AMP (cGAMP).

Results: DENV infection of A549 cells resulted in greater cGAMP production, and infection of cGAS-silenced A549 cells resulted in greater DENV replication compared to un-silenced A549 cells, both suggesting activation of cGAS and downstream interferons by DENV. Plating of BHK21 cells at low density or treating these cells with CBX, a gap junction inhibitor, before infection also led to increased DENV replication, which shows that cGAMP is transmitted between cells through gap junctions. Infection of A549 cells followed by mitochondrial staining indicated that mitochondrial aggregation occurs, a phenomenon that correlates with mitochondrial damage. Finally, infection of A549 cells with DENV followed by measurement of mtDNA in the cytosol revealed higher cytosolic mtDNA levels post-infection, a likely sequela of mitochondrial damage.

Conclusions: Our results suggest that the +ssRNA virus, DENV, activates cGAS by inducing mitochondrial damage, thereby allowing mtDNA to escape into the cytosol and act as an endogenous substrate of cGAS, triggering downstream interferon production. As the most effective vaccines require strong interferon induction, activation of cGAS may potentially be used as a marker for efficacy in the development of next-generation dengue vaccines.
Exploring the Vagueness of Religion & Spirituality in Complex Pediatric Decision-Making: A Qualitative Study

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Background: Advances in life-sustaining therapies have led to new challenges in decision-making for parents of seriously ill children. Many parents say religion and spirituality (R&S) influence their decisions, but the mechanism and outcomes of this influence are unknown. Health care providers (HCPs) often feel unprepared to discuss R&S with parents or address conflicts between R&S beliefs and clinical recommendations (e.g. reluctance to withdraw life-sustaining therapy due to a belief in miracles). Prior research on the role of R&S in pediatric palliative care has identified important R&S themes but has failed to clarify how R&S influence decision-making. Our study sought to illuminate the influence of R&S on parental decision-making and explore how HCPs interact with parents for whom R&S are important.

Methods: A longitudinal, qualitative descriptive design was used to (1) identify R&S factors affecting parental decision-making, (2) observe changes in R&S over time, and (3) learn about HCP perspectives on parental R&S. The study sample includes 16 cases featuring infants with complex life-threatening conditions. Each case included one or more infants, at least one parent, and at least one HCP (physicians, nurses, nurse practitioners, and social workers). Data from each case consisted of the infant’s medical records and sets of longitudinal one-on-one interviews with mothers, fathers, and HCPs. Thematic analysis was performed on 362 narrative interviews to identify R&S themes and content related to decision-making. Content was then reviewed to characterize the relevance of identified themes to decision-making, observe changes over time, and compare R&S content derived from HCP and parent interviews.

Results: Parents from 13 cases reported R&S influenced decision-making. Most HCPs were unaware of this influence. Fifteen R&S themes appeared in parent and HCP transcripts. Themes were organized into four categories: Values/Beliefs, Practices, People, and Emotions. The themes most often associated with decision-making were Hope & Faith, God is in Control, Miracles, and Prayer. R&S influenced decisions about treatment initiation, procedures, and life-sustaining therapy, but the ultimate impact of R&S factors on these decisions varied.

Conclusions: Parents consider R&S fundamental to decision-making, but apply R&S concepts in vague ways, suggesting R&S impact how decisions are made more than what decisions are made. Lack of clarity in parental expressions of R&S does not necessarily indicate insincerity or underestimation of the seriousness of a child’s prognosis; R&S can be applied to decision-making in both functional and dysfunctional ways. We present three models of how religious and spiritual vagueness functions in parental decision-making and offer practical applications for HCPs. If HCPs can recognize how R&S is functioning in a particular case, they may be better able to communicate with families, address their R&S needs, and support their decision-making process.
Genital Mycoplasmas and Vaginal Fluid Antimicrobial Peptides in Pregnancy

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Background: Genital mycoplasmas are associated with multiple adverse pregnancy outcomes including preterm birth, premature rupture of membranes, chorioamnionitis, endometritis, cesarean wound infections, and neonatal infectious disease. In response to pathogenic microbes, the vaginal immune system produces antimicrobial peptides (AMPs). Altered vaginal levels of AMPs have been associated with bacterial vaginosis and genital infections in pregnancy. Disruption of antimicrobial function in the cervicovaginal system can predispose to intrauterine infections and inflammatory infiltration, common prefaces for maternal and neonatal complications. We evaluated the association between four species of genital mycoplasmas, vaginal fluid AMPs, and adverse pregnancy outcomes.

Methods: Cervicovaginal swabs were self-collected by 120 women with singleton, non-anomalous intrauterine pregnancies between 16 and 22 weeks gestation. All samples were tested for *Mycoplasma hominis*, *M. genitalium*, *Ureaplasma urealyticum*, and *U. parvum* using real-time PCR, as well as assayed for vaginal fluid defensins. Defensin levels were compared between women without any genital mycoplasmas, women with *Ureaplasma spp* only, and women with both *Mycoplasma spp* and *Ureaplasma spp*. Baseline demographic, pregnancy outcome, and neonatal outcome data were collected. Statistical analyses of baseline characteristics and defensin levels were performed with Kruskal–Wallis and Fisher’s exact tests, and a linear regression model was used to assess the relationship between genital mycoplasmas and defensins. A p-value of <0.05 was used to determine statistical significance.

Results: In this cohort, one or more species of genital mycoplasmas were detected in 55.8% of women. *U. parvum* was the most prevalent species (n=58; 48.3%), whereas *M. genitalium* was the least prevalent (n=3; 2.5%). Overall, there was no significant difference in median defensin levels detected among women without any genital mycoplasmas (3441.3 ng/ml; IQR 2165.6–4370.2 ng/ml), women with *Ureaplasma spp* only (2718.2 ng/ml; IQR 1811.4–3911.4 ng/ml), and women with both *Mycoplasma spp* and *Ureaplasma spp* (3755.1 ng/ml; IQR 2638.4–4894.7 ng/ml; p=0.20). These results were not affected after controlling for maternal race (p=0.77).

Conclusions: Our results demonstrate that genital mycoplasmas are prevalent in pregnant women. However, we did not find a significant difference in defensin levels when comparing women with and without genital mycoplasmas, indicating that other underlying mechanisms may be contributing to the regulation of defensins in women with genital mycoplasmas. Further studies with larger cohorts of patients are warranted for a more refined understanding of pathogenic microbes, host response, and pregnancy outcomes.
Background: Research suggests a positive relationship between high-fat dairy, particularly whole milk, and prostate cancer mortality. However, data are limited regarding intake among men, after prostate cancer diagnosis.

Methods: We conducted a prospective study among 1,336 men with non-metastatic prostate cancer in CaPSURE. The men answered a food frequency questionnaire (FFQ) in 2004-2005 (median time from diagnosis to the FFQ: 2 y) and were followed until April 2016 for prostate cancer recurrence, defined as: prostate cancer death, bone metastases, biochemical recurrence, or secondary treatment. Multivariate Cox proportional hazards regression was used to calculate hazards ratios (HR) and 95% confidence intervals (CI) for associations between whole and low-fat milk; total, high-fat, and low-fat dairy; and other specific dairy items and prostate cancer recurrence.

Results: 139 events were observed (mean follow-up: 7.2 y). Men who consumed whole milk >4 times/week had an 80% increased risk of prostate cancer recurrence compared to men who consumed whole milk 0-3 times/month (HR: 1.80; 95% CI: 1.05, 3.11; p-value: 0.03). BMI modified the association between whole milk intake and risk of prostate cancer recurrence (p-interaction=0.007). Among men with a BMI ≥27 kg/m², men who reported >4 servings/week vs. 0-3 servings/month of whole milk had a 3.4-fold higher risk of prostate cancer recurrence (HR: 3.38; 95% CI: 1.81, 6.34; p-value: <0.001). No association was seen in men with BMI<27 kg/m². Low-fat milk and other dairy foods were not associated with prostate cancer recurrence.

Conclusions: Whole milk consumption after prostate cancer diagnosis was associated with prostate cancer recurrence, particularly among very overweight or obese men. Men diagnosed with non-metastatic prostate cancer who choose to drink milk should select non-fat or low-fat options.
Effect of Increased Fluid Intake on 24-hour Urinary pH in Stone Formers with Low Urine Volume

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**Background:** Low urinary pH is a known risk factor for kidney stones and is routinely managed through dietary and medical treatment. First-line conservative dietary recommendations, such as increased fluid intake, decrease overall stone risk, but little is known about how an improvement in urine volume affects the urinary pH. Our aim was to assess the change in urinary pH associated with increased fluid intake in the absence of directed urine alkalinizing therapy. We hypothesize that increased fluid intake in patients with low urine volume and low urinary pH will result in an improvement in urinary pH.

**Methods:** We queried a retrospectively-maintained database of 24-hour urine analyses of 2,197 kidney stone formers from 2000 to 2015. Inclusion criteria included age ≥18, multiple 24-hour urine analyses, initial and subsequent analyses obtained ≥30 days apart, and both low urine volume (<2L/24h) and pH (<6.5) on initial collection. Patients treated with thiazide diuretics or alkalinizing agents were excluded. Initial and subsequent 24-hour urine analyses were examined to evaluate for a change in 24-hour urine parameters. Pre- and post-intervention means were compared using Student’s T-test. Univariate and multivariate analyses were performed to determine variables which predict an adequate change in urinary pH (≥6.0) on second 24-hour urine analysis. A multivariate model was constructed using manual stepwise methods.

**Results:** Using the inclusion and exclusion criteria, 169 patients were identified (96 male, 73 female). The mean 24-hour urine volume increased from 1.30L pre-intervention to 2.13L post-intervention (p<0.001). The mean 24-hour urinary pH increased from 5.72 pre-intervention to 6.15 post-intervention (p<0.001). Urinary citrate also increased from 448.07 pre-intervention to 618.14 post-intervention (p<0.001). Urinary NH4, sulfate, and urea nitrogen showed no significant decrease. Multivariate analysis produced a best-fit model utilizing initial urine volume, initial pH, initial ammonium, change in urine volume, change in citrate, and change in ammonium. This model demonstrates a correlation between increase in urine volume and increase in urinary pH in this population.

**Conclusions:** We conclude that increasing fluid intake as part of conservative dietary measures in stone formers with low urine volume and urinary pH resulted in significant improvement in urinary pH in certain patients, providing further explanation for the protective effect of increased urine volume on stone risk. Given the ability for this model to output a probability of favorable pH results based on initial urinary parameters, it could potentially be used to assist in predicting response to fluid therapy in patients.
The B cell repertoire and antibody maturation elicited by adjuvanted HIV envelope vaccines in infants

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Background: We have previously reported that infants immunized with an MF59-adjuvanted rgp120 vaccine developed a greater magnitude and longer duration of potentially protective anti-V1V2 IgG responses than adults from the moderately effective RV144 trial (ALVAC prime/Alum-adjuvanted AIDSVAX boost strategy). To determine if these distinct vaccine responses are due to inherent differences in the adult and infant immune systems, we compared Env-specific IgG responses in adults and infants immunized with the same MF59-adjuvanted rgp120 vaccine. We then isolated and characterized the epitope specificity and immunogenetic characteristics of infant vaccine-elicited monoclonal antibodies (mAbs).

Methods: The magnitude and duration of IgG response against gp120 and the V1V2 region were measured in adult (AVEG 201 trial) and infant (PACTG 230 trial) vaccine recipients using a binding antibody multiplex assay (BAMA). Binding and avidity against a clade B V2 peptide were assessed by ELISA. Antigen-specific memory B cells from five infant vaccines were sorted via flow cytometry, followed by RT-PCR, gene sequencing and 293T cell transfection for mAb production. Infant mAb immunogenetic characteristics (VH gene usage, CDR3 length, mutation rate) and epitope specificity were then evaluated.

Results: At peak immunogenicity, the magnitude of Env-specific IgG responses was higher in vaccinated infants than in adults (MNgp120 median MFI: infants 15,509, adults 2290; p less than 0.001). Moreover, potentially protective V1V2-specific IgG binding was greater than one log higher in vaccinated infants compared to adults (median MFI: infant 23926, adult 1538; p less than 0.001) and remained higher 6-7 months post-peak immunogenicity (median MFI: infants 2523, adults 11; p equals 0.018). The avidity index (AI) of V2-specific IgG was comparable at peak immunogenicity between adults and infants (mean AI: infant 0.6, adult 0.56; p equals 0.46). Out of 66 functional mAbs isolated from 5 infants, 31 were specific for the gp120 envelope region with the following epitope specificities: 11 CD4-binding site, 11 undetermined, 4 V1V2 loop, 2 V3 loop, 2 multi-epitope. Vaccine-elicited mAb heavy chains contained relatively long CDR3 regions (median 18 amino acids), but displayed low levels of somatic gene mutation (median 2.3 percent).

Conclusions: Our findings suggest that infant responses to HIV Env immunogens are equal or higher in magnitude and durability to those of adults. These results underline the utility to test promising HIV vaccine candidates in pediatric populations. In future works, infant mAbs will be assessed for antiviral function (ADCC and neutralization assays) and their characteristics compared to adult vaccine-elicited mAbs.
Protocolized Hemostatic Factor Use in Major Thoracic Aortic Surgery

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Background: The role of purified hemostatic factor concentrates in the management of perioperative bleeding after cardiac surgery remains controversial, mainly due to concerns for thromboembolic complications. We hypothesized that administration of a low dose of recombinant factor VIIa (rFVIIa) and, in cases of continued refractory bleeding, 10-15 units/kg of 3-factor prothrombin complex concentrate (PCC) would allow for reversal of coagulopathy without high rates of thromboembolic complications. As such, the purpose of this study was to describe our experience with protocolized use of rFVIIa and PCC following major thoracic aortic surgery.

Methods: All patients (n = 1569) in a prospectively maintained institutional aortic surgery database who underwent elective and non-elective major thoracic aortic surgery (root/ascending, arch, or descending/thoracoabdominal) from 2005-2016 were reviewed. Patients who received intra- or postoperative (within 4 hours of intensive care unit arrival) purified hemostatic factor concentrates (rFVIIa and/or PCC) were identified. The primary endpoint was thromboembolic complications. Secondary endpoints included 30-day/inpatient mortality, bleeding complications, and organ-specific morbidity.

Results: A total of n = 408 (26%) patients received intra- or postoperative purified hemostatic factor concentrates (in addition to other pharmacological agents and transfusional therapies) that included rFVIIa only (n = 277, 18%), PCC (three-component) only (n = 59, 4%), or both (n = 72, 5%). Median patient age was 60 years and 41% had undergone prior aortic surgery; 41% underwent surgery for an aortic dissection indication, 33% were non-elective cases, and hypothermic circulatory arrest was used in 80%. The most common indication for using rFVIIa and/or PCC was severe coagulopathy post cardiopulmonary bypass. Most patients received low-dose hemostatic factors. Clinical outcomes were excellent with low incidences of reoperation for bleeding (n = 18, 4%) and few thromboembolic complications, the highest of which was embolic stroke (n = 11, 3%). As a result of this cumulative experience, we altered our existing institutional bleeding management algorithm by moving low dose rFVIIa administration to earlier and by adding standardized administration of low dose PCC in the setting of ongoing bleeding with coagulopathy.

Conclusions: Low dose rFVIIa and PCC were associated with reversal of coagulopathy without evident thrombosis when administered for the treatment of bleeding and coagulopathy in major thoracic aortic surgery. As such, their use should be considered in institutional bleeding management algorithms.
Rapid Valproic Acid Induced Modulation of the Traumatic Proteome in Porcine Model of Hemorrhagic Shock and Traumatic Brain Injury

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Background: Histone deacetylase inhibitors like valproic acid (VPA) improve survival in lethal models of hemorrhagic shock and polytrauma. Although VPA is known to modulate transcription, its ability to reduce mortality within minutes of administration suggests a more rapid mechanism is involved. We hypothesized that VPA treatment would cause proteomic changes within an hour of treatment and that structural and/or effector proteins would be differentially affected with respect to protein quantity or post-translational modifications.

Methods: We utilized a porcine model of hemorrhagic shock (40% blood loss) plus traumatic brain injury (controlled cortical impact, 12 mm penetration). Animals were kept in shock for 2 hours during which they were assigned to two groups (n=3): VPA (150 mg/kg) + Normal Saline (VPA+NS; NS volume = 3:1 shed blood volume) or 3:1 NS alone. Peripheral blood mononuclear cells (PBMCs) were collected at: baseline, post-shock, and post-resuscitation (30-minutes after VPA infusion). Proteomic profiles of PBMCs were measured using 1D-gel electrophoresis, liquid chromatography, mass spectrometry, and analyzed with Ingenuity Pathway Analysis (IPA) software.

Results: The VPA+NS group demonstrated significant proteomic changes compared to NS. Quantitative analysis found differences in over 200 proteins including effector, regulatory, and structural proteins in critical cell signaling pathways. Additionally, we demonstrated VPA-induced differential acetylation of lysine residues on histone and non-histone proteins. Finally, using IPA, we showed significant increases in numerous pro-survival and cytoskeletal intracellular pathways including: Rho GTPase signaling (p=1.66E-11), integrin signaling (p=4.19E-21), and a decrease in RhoGDI signaling (p=4.83E-12).

Conclusions: In a porcine model of severe injuries, VPA treatment is associated with protective changes in the proteome that are measurable within minutes of treatment.
Female Sex Diminishes Hypertensive Response of Vascular Type 1A Angiotensin Receptors

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**Background:** Angiotensin (Ang) II is a major mediator of hypertension pathogenesis and end organ damage. In addition, there are well-documented differences in expression of the renin angiotensin system (RAS) components and Ang II responses between males and females, which may explain gender differences in BP and hypertension epidemiology. We have previously shown that AT1A receptors in vascular smooth muscle cells (VSMCs) play a critical role in BP regulation and hypertension pathogenesis, but these studies were carried out exclusively in male mice.

**Methods:** To assess the contribution of vascular AT1A receptors in females, we utilized female mice with cell-specific deletion of AT1A receptors in smooth muscle cells (SMKO mice) using Cre-loxp technology. We evaluated for differences between control and SMKO mice in baseline blood pressure, salt sensitivity, cardiac hypertrophy, chronic angiotensin II-dependent hypertension, natriuresis, baseline renal tissue perfusion, as well as systemic vascular responses and renal tissue perfusion following acute angiotensin II infusion. These responses were compared to male responses. Analyses were performed using unpaired t tests and ANOVA.

**Results:** Similar to our studies in male mice, elimination of vascular AT1A receptors in females caused a reduction (~8 mmHg) in baseline BP. However, unlike previous findings in males, sodium sensitivity was unaffected in female SMKO mice. Likewise, the severity of Ang II–dependent hypertension was not diminished during the early phase of Ang II infusion in females, compared to the marked reduction in Ang II-hypertension we had observed in male SMKO mice. In contrast, during the last two weeks of chronic Ang II infusion, resistance to hypertension was seen in the female SMKO mice, with a ≈33% reduction in BP compared to controls. Similar to males, there was a virtually complete elimination of Ang II-dependent renal hemodynamic responses in female SMKOs, but unlike males, acute vasoconstrictor responses in the systemic vasculature were further diminished in female SMKO mice.

**Conclusions:** Here we show that vascular AT1A receptors play an important role in determining baseline BP and the hypertensive response to Ang II. However, distinct differences were identified for how these effects are mediated in female mice as compared to male mice. For instance, female vascular AT1A receptors have a more pronounced effect on peripheral vascular resistance without altering natriuresis. Further elucidation of the mechanisms mediating these effects will be important to identifying more precise therapy for treatment of hypertension and end-organ damage.
Unexpected Cardiac MRI Findings in Patients Presenting to the 
Emergency Department for Potential Acute Coronary Syndrome

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Background: Cardiac magnetic resonance imaging (CMRI) has become increasingly used in 
patients presenting to the emergency department (ED) with symptoms concerning for acute 
coronary syndrome (ACS). We hypothesized that CMRI detects a number of alternative 
diagnoses (diagnoses other than ACS that could plausibly explain symptoms) and incidental 
findings unrelated to ACS in these patients. These unexpected findings could influence 
patient management by establishing diagnoses or by requiring further testing.

Methods: We prospectively enrolled adult patients who presented to an academic ED from 
2011 through 2015 for possible ACS, had no signs of ischemia on initial EKG, had at least 
one negative cardiac biomarker, and subsequently had a CMRI as part of their diagnostic 
evaluation. All medical charts were reviewed to verify accurate prospective data collection 
and collect follow-up data. Interrater reliability was established with a second independent 
reviewer reviewing 10% of the total number of charts. Standardized interpretations from the 
attending physician were used for the CMRI diagnostic findings with automatic download of 
results from an ongoing database. Basic descriptive statistics were calculated.

Results: A total of 391 patients were included. The median age was 59.0 years, 44.0% were 
male, and 43.7% were African American. The CMRI was read as normal for CAD-related 
findings in 285 (72.9%) patients. Abnormalities attributable to CAD were found in 106 
(27.1%) of patients. Of these 106 patients, 35 (33.0%) had no known history of CAD. 
Amongst these 106 patients with CAD-related abnormalities, 42 (39.6%) had ischemia on 
stress perfusion imaging. The other 64 (60.4%) patients with CAD-related abnormalities had 
MI without ischemia. 54.7% of these patients had no known history of prior MI. Previously 
undiagnosed moderate to severe valvular disease was the most common non-CAD cardiac 
finding, occurring in 20 (5.1%) cases. There were also 4 (0.9%) new cases of hypertrophic 
cardiomyopathy, 1 (0.3%) new case of non-ischemic cardiomyopathy, and 1 (0.3%) new case 
of mixed ischemic and non-ischemic cardiomyopathy. Other alternative diagnoses were rare 
with 1 case of aortic aneurysm, 1 case of aortic dissection, 1 case of acute myocarditis, 3 
cases of pericarditis, and 2 cases of moderate pleural effusion. Cardiac incidental findings 
were rare with one myxoma and 2 moderate pericardial effusions diagnosed. A total of 79 
patients (20.2%) had extracardiac incidental findings. Of these incidental findings, the 
interpreting physician recommended further imaging in 43 patients; however, only 8 (18.6%) 
of these patients had follow-up imaging in our electronic medical record system.

Conclusions: This experience suggests that CMRI is useful not only in diagnosing 
symptomatic CAD but also potentially important non-CAD related disease. These factors 
may impact their use in ED-based ACS workups.
Cell Fusion in the Drosophila Hindgut Facilitates Aneuploidy Tolerance

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**Background:** Aneuploidy, or aberrant chromosome number, is associated with various cancers and birth defects. Previous work in the Fox laboratory found that cells of the *Drosophila melanogaster* rectum tolerate a surprisingly high level of aneuploidy. In parallel, we discovered that the rectum forms a syncytium during pupation, which led us to hypothesize that syncytium formation allows for aneuploidy tolerance in these rectal papillae.

**Methods:** We undertook a genetic screening approach to discover new, *in vivo*-relevant functions/mechanisms of aneuploidy tolerance. This was done using a haploinsufficiency screen of 465 haploinsufficiency lines covering the entire genome of the fly. To identify regulators of the syncytium formation that may be important for aneuploidy tolerance, we screened the aneuploid-specific lethal lines from the initial screen using a dual-color fluorescence-based assay (Brainbow) that enables us to detect animals with defective cell fusion.

**Results:** From the haploinsufficiency screen which covered 2/3 of the genome, 42 lines were aneuploid-specific lethal, uncovering new candidate regulators of a cellular response to aneuploidy. These lines were subsequently looked at with Brainbow. 44 haploinsufficiencies were tested, of which 9 disrupted syncytium formation. Mutants with smaller deletions in the genome coded by the 9 positive results were tested as well. Of the 25 narrowed down haploinsufficiencies, 5 were positive hits. 44 RNAi lines were tested based on results found from the narrowed down haploinsufficiencies and from candidate intercellular protein sharing genes, 2 of which were positive hits – Vacuolar H+ Atpase 16 (Vha16) and Rab11. Vha16 and Rab11 are involved in the phagolysosomal pathway. Rab11 facilitates the creation of early phagosomes and lysosomes. Vha16 is involved in their maturation by acidification of these vesicles. Thus, vesicle acidification may be critical in rectal cell fusion.

**Conclusions:** We propose that the phagolysosomal pathway interacts with the lateral membrane of *Drosophila* rectum to create intercellular bridges during metamorphosis, forming the syncytium during adulthood. These fusion events may mediate aneuploidy tolerance. In summary, we have conducted a genetic screen that has identified novel regulators of an aneuploidy tolerance mechanism, one which may involve vesicle-mediated cell-cell fusion.