University of Wisconsin School of Medicine and Public Health

8th Annual Medical Student Research Forum

January 19, 2010

PROGRAM and ABSTRACTS

Support for 8th Annual Medical Student Research Forum is provided by the Office of Academic Affairs and the Herman and Gwendolyn Shapiro Foundation
8th Annual Medical Student Research Forum

Tuesday, January 19, 2010 • Noon to 5:30 pm

12:00-1:00 PM
HSLC Atrium

1:00 PM
1306 HSLC

Welcome and Introduction
Robert N. Golden, MD
Dean and Vice Chancellor for Medical Affairs

1:15 PM
1306 HSLC

SHAPIRO GUEST LECTURE

Considering Research:
Approaching Adolescent Health Care through Media and Technology

Megan Moreno, MD, MEd, MPH
Assistant Professor, Department of Pediatrics
UW School of Medicine and Public Health

Life during medical school and residency is busy and provides many challenges while learning how to provide patient care. In the context of her research interests in adolescent medicine, Dr. Moreno will explore ways in which pursuing research can augment student clinical learning as well as the capacity to improve health care. Dr. Moreno’s research focuses on novel ways to prevent and intervene to reduce major causes of morbidity and mortality in the adolescent population. One particular area of interest is adolescents’ use of media and technology and how these may impact adolescent health behaviors. Dr. Moreno has investigated adolescents’ use of social networking web sites, such as MySpace and Facebook, and ways in which adolescents display information about their health and behaviors on these public web profiles. Her work also involves how to provide adolescents access to online health systems.

Megan Moreno attended Northwestern University for her undergraduate degree, George Washington University for her MD. She completed a pediatric residency and a chief resident year at UW Madison, and during this time she also completed a Masters in Education degree from UW. Dr Moreno completed an adolescent medicine fellowship and an MPH from the University of Washington (the “other” UW) in Seattle before returning to UW Madison as an Assistant Professor. Dr Moreno’s research is currently supported by the Center for Women’s Health Research at UW, as well as by the NIAAA.

2:30 PM
1306,1325,1345 HSLC

Student Research Oral Presentations

4:00-5:30 PM
HSLC Atrium

Reception and Student Research Poster Session
Student Oral Presentations
Sessions run concurrently from 2:30-4:00pm

Session A
Room 1306 HSLC
Faculty Facilitator: Herb Chen, MD, FACS

Wall Shear Stress Analysis of Ascending Aortic Aneurysms Using PC-VIPR
Student: Erik Bieging
Mentor: Christopher François, MD
UW Department of Radiology

A Window of Opportunity and the Problem of Predicting the Value of Future Health States: Case Report and Ethical Analysis of Traumatic Quadriplegia
Student: Abigail Taub
Mentor: Margaret Schwarze, MD
UW Department of Surgery

Thoracic Muscle Flap Outcomes
Student: Francisco Castro
Mentor: Michael Bentz, MD
UW Department of Surgery, Division of Plastic and Reconstructive Surgery

Contributions of Preconception Care to Decreased African American Infant Mortality in Dane County from 1997 to 2007
Students: Leah Haglund and Taya Schairer
Mentor: Lee Dresang, MD
UW Department of Family Medicine

Calculating Wall Shear Stress in the Basilar Artery of Healthy Volunteers Using Automated Spline Interpolation and PC-VIPR, a Fast, Radial, Undersampled 3-D PC-MRA Technique
Student: Warren Chang
Mentor: Patrick Turski, MD
UW Departments of Radiology and Medical Physics

ZV/ZV’ and ZIIR Elements of the BZLF1 Promoter of Epstein-Barr Virus Function Synergistically to Establish and Maintain Latency
Student: Patrick McCarthy
Mentor: Janet Mertz, PhD
UW Department of Oncology, McArdle Laboratory for Cancer Research
Session B
Room 1345 HSCL
Faculty Facilitator: John Harting, PhD

*Parathyroid Hormone Deficiency After Total Thyroidectomy: Incidence and Time to Resolution*

Student: Linda Youngwirth  
Mentor: Herbert Chen, MD, FACS  
UW Department of Surgery, Section of Endocrine Surgery

*Impact of Tumor Location on Morbidity and Mortality: A Retrospective FMRI Study*

Student: Joel Wood  
Mentor: Vivek Prabhakaran, MD, PhD  
UW Department of Radiology

*Acoustoeastography of the Acetabular Labrum*

Student: Walker Flannery  
Mentor: James McCarthy, MD  
UW Department of Orthopedics and Rehabilitation

*Medical Student Attitudes Regarding Pharmaceutical Companies and Exposure to Their Influence—A 2009 Survey of UWSMPH*

Students: Cody Soyk  
Mentor: Richard Rieselbach, MD  
UW Department of Medicine

*Utility of MicroRNA Profile for Predicting Recurrence of Rectal Cancer*

Student: Alex Riordan  
Mentor: Gregory Kennedy, MD, PhD  
UW Department of Surgery, Section of Colon and Rectal Surgery

*Chloride Cotransporters Involved in the Development of Chronic Neuropathic Pain Following Spinal Cord Injury*

Student: Tera Hasbargen  
Mentors: Daniel Resnick, MD; Gurwattan Miranpuri, PhD; Dandan Sun, PhD  
UW Department of Neurological Surgery
Session C  
Room 1325 HSCL  
Faculty Facilitator: Patrick McBride, MD, MPH

Developing a Tool to Evaluate State Prescription Monitoring Programs  
Student: Callie Hansen  
Mentor: June Dahl, PhD  
UW Department of Pharmacology, Wisconsin Pain Initiative

Activation of Systemic Inflammatory Events Following Brain Death  
in a Non-Human Primate Model  
Student: Alexander Froyshteter  
Mentor: Luis Fernandez, MD  
UW Department of Surgery

Language Lateralization in Brain Tumor Patients:  
A Retrospective FMRI Study  
Student: Amy Utter  
Mentor: Vivek Prabhakaran, MD, PhD  
UW Department of Radiology, UW Institute for Clinical and Translational Research

Patient Expectations of Physicians Concerning Cost of Care  
Students: Erika Ruud  
Mentor: Sarah Davis, JD, MPA  
Center for Patient Partnerships, UW-Madison

Resveratrol Induces Notch2, Suppresses Growth, and Decreases  
Neuroendocrine Markers in Medullary Thyroid Cancer  
Student: Matthew Truong  
Mentor: Herbert Chen, MD, FACS  
UW Department of Surgery

Trends in Bariatric Surgery For Morbid Obesity  
in Wisconsin: A Six Year Follow-Up  
Student: Dana Henkel  
Mentors: Jon Gould, MD; Patrick Remington, MD  
UW Department of Surgery; UW Department of Population Health Sciences
Title: WALL SHEAR STRESS ANALYSIS OF ASCENDING AORTIC ANEURYSMS USING PC-VIPR

Authors: Erik Bieging, MS; Ben Landgraf, BS; Kevin Johnson, PhD; Oliver Wieben, PhD; Alex Frydrychowicz, MD; Christopher François, MD

Department: Department of Radiology, UW School of Medicine and Public Health

Mentor(s): Christopher François, MD

Support: Shapiro Summer Research Program and Department of Radiology

Background: Wall shear stress (WSS) has been shown to play a role in aneurysm formation and endothelial cell function. 4D Phase Contrast (PC) MRI can be used to estimate WSS in vivo in a number of blood vessels. PC MRI with 3D radial undersampling (PC VIPR) enables acquisition of 4D flow datasets with increased spatial resolutions in a reasonable scan time, potentially allowing for improved WSS estimation. The purpose of this study was to compare time resolved WSS in patients with ascending aortic aneurysms (AscAA) with that in normal volunteers.

Methods: PC VIPR MRI data were acquired in 11 patients with AscAA and in 10 healthy volunteers. Data were reconstructed into 20 time frames over the cardiac cycle using retrospective ECG-gating. The surface of the ascending aorta was manually segmented based on complex difference image data using a cubic-spline based interpolation algorithm. Each ascending aorta surface was divided radially and horizontally. WSS was calculated at each individual surface point and then averaged over the vessel surface for each time point to find WSS as a function of time. From each WSS-time function five parameters were extracted and statistically compared: time averaged WSS, peak systolic WSS, time of peak WSS, diastolic baseline WSS, and percent increase in WSS from baseline to peak.

Results: The WSS-time curves in patients with AscAA show a slower onset and prolonged duration of systolic WSS. Although time-averaged WSS was higher and the peak systolic WSS was lower in patients than controls, the results were not statistically significant. Time of peak WSS occurred significantly later in the cardiac cycle, diastolic baseline WSS was significantly increased, and percent increase from baseline to peak was significantly reduced in the aneurysm group (all P<0.05). When the 4 walls of the ascending aorta were studied, the aneurysm group’s anterior wall showed increased peak WSS without significant change in baseline WSS.

Conclusions: Use of time resolved 3D vessel surface segmentation with PC VIPR datasets allowed for investigation of WSS dynamics over the cardiac cycle and showed that AscAA are associated with alterations in WSS. Individuals with AscAA have increased WSS during diastole, reduced change in WSS over the cardiac cycle, and delayed onset of WSS in systole compared to individuals with normal aortic anatomy. Spatial patterns of WSS in AscAA show differences from normal ascending aortas. Further investigation of WSS in aneurysms may help to better define the relationship between WSS and aneurysm formation.
Title: A WINDOW OF OPPORTUNITY AND THE PROBLEM OF PREDICTING THE VALUE OF FUTURE HEALTH STATES: CASE REPORT AND ETHICAL ANALYSIS OF TRAUMATIC QUADRIPLEGIA

Authors: Abigail L Taub, BS; Margaret L Schwarze, MD

Department: Department of Surgery, UW School of Medicine and Public Health

Mentor(s): Margaret L Schwarze, MD

Support: Shapiro Summer Research Program and Department of Surgery

Background: A 38 year-old man was transferred to our trauma center after a fall from standing had caused a C2-3 fracture-spondylolisthesis. The patient suffered a cord compression that caused complete neuroparalysis at C3 and resulting ventilator dependent quadriplegia. In the first few hours after his injury the patient required aggressive life-sustaining therapy for neurogenic shock and aspiration pneumonia. During this initial treatment phase the patient and his family requested withdrawal of life-supporting therapy confirming the patient’s prior statements regarding his desire to not live with quadriplegia.

Methods: Review of the medical literature regarding care for patients with quadriplegia and ethical concepts including; decision-making capacity, window of opportunity, withholding versus withdrawing therapy, respect for autonomy and prediction of future health states. Ethical analysis of clinical options for the patient’s care provider was performed.

Results: Surgeons treating unstable patients with new onset traumatic quadriplegia who request withdrawal of life supporting therapy have three options; Withdraw support in the initial treatment period, continue supportive therapy for a brief (10-14 days) and mutually agreed upon time, continue supportive therapy for no less than 6 months so that the patient can obtain knowledge about quality of life as a person with quadriplegia. There is significant tension between the imperative of respect for patient autonomy and the patient’s ability to accurately predict the quality of life for future health states, which may interfere with his decision-making capacity. This tension is exaggerated by the perception of a window of opportunity whereby patients and their surrogates favor withholding life-supporting therapy (vasopressors) over withdrawal of life-supportive measures (ventilators).

Conclusions: The surgeon is uniquely challenged by the patient with traumatic quadriplegia to both respect patient autonomy and prevent an irreversible decision that may not ultimately be consistent with patient preferences. It is difficult for patients to accurately predict the quality of life of future health states. Thus, a significant decision may best be made after the patient has had time to fully weigh his options. Although concerns about being stuck in a life which is unacceptable when the patient is rescued from his immediately life threatening injury during a perceived “window of opportunity” may dominate the discussion, surgeons may resist the pressure to make a hasty decision. If the patient prefers death over life as a quadriplegic in the near or far future, life supporting therapies including ventilatory support, hydration and nutrition can be removed.
Background: The incidence of empyema in patients following a pulmonary resection is 2-16%. These are conservative estimates based on complications arising immediately following a surgery. Thus, the actual incidence is believed to be much higher. Thoracomyoplasty, the transposition of extrathoracic muscle flaps into the intrathoracic defect, has become the gold standard for the management and prevention of empyemas. Thoracomyoplasty is also employed for the treatment of bronchopleural fistulas, mediastinitis, sternal wounds, and other thoracic wall defects. The success of the procedures involves the excellent antibiotic delivery by the highly vascularized muscle flaps.

Large-scale studies typically show an average postoperative hospital length of stay (LOS) ranging from 14 to 15.7 days, with a 30-day post-surgical survival rate of 93%-94.7%. Despite the abundance of literature citing the success rates of thoracomyoplasty, there is little comprehensive data that correlate specific treatment practices with positive patient outcomes as measured by shorter postoperative LOS, survival rates and morbidity indices. Thus, the goal of this study is to identify treatment practices that correlate with positive patient outcomes.

Methods: A retrospective review of 72 consecutive patients who underwent thoracomyoplasty by a single plastic and thoracic surgical team between 1998 and 2009 was performed. Patient demographics, surgery type, muscle flaps used, complications and pre and post-operative treatments were noted. Outcomes were predominantly assessed by the post-operative LOS, 30-day post-operative survival rate, and the rate of complications.

Results: 72 consecutive patients underwent thoracomyoplasty procedures. Of these, 49 were male and 23 were female. The average age was $57.54 \pm 16.07$ years (age range 30 days-83 years). The post-operative LOS was $15.53 \pm 24.29$ days. The 30 day post-operative mortality rate was 2.8%. Five patients died post-operatively prior to discharge. The primary reasons for surgical involvement were open-chest wounds (59.7%), empyemas (23.6%), and bronchopleural fistulas (13.9%). 27 patients were treated with a single muscle flap, 37 required two flaps, and 8 patients required three. The three most common muscle flaps used were the right latissimus dorsi, right anterior serratus, and bilateral pectoralis major muscle flaps. At the time of the study 50 patients were alive and 22 were deceased.

Conclusions: The post-operative length of stay falls is comparable to those reported by other large-scale studies. The 30-day post-surgical is also similar to that of other studies. Given the thorough review of medical charts in this study, it is hoped that further analyses of this data will identify specific treatment practices that correlate with positive patient outcomes.
Title: CONTRIBUTIONS OF PRECONCEPTION CARE TO DECREASED AFRICAN AMERICAN INFANT MORTALITY IN DANE COUNTY FROM 1997 TO 2007

Authors: Leah Haglund, BS; Taya Schairer, BS; Lee Dresang, MD

Department: Department of Family Medicine, UW School of Medicine and Public Health

Mentor(s): Lee Dresang, MD

Support: Department of Family Medicine Summer Student Research and Clinical Assistantship, MERC

Background: In 2004, the US infant mortality rate was 6.78 per 1000 live births while the black infant mortality rate (BIMR) was 13.25 per 1000 live births. In Dane county, African American infant mortality has decreased 70% since the 1990’s while in other areas, such as Racine County, have not seen such declines. To try to reduce infant mortality disparities in Wisconsin, the project aims to identify factors related to birth outcome.

Methods: A clinical chart review was performed at the Wingra and Northeast clinics in Dane County, which compared births from 1997/1998 and 2007. Study participants were selected based on records from the University of Wisconsin Department of Family Medicine Data Warehouse, which identified them as African Americans who gave birth within the designated years. Information on preconceptual care including management of medical conditions, perinatal consultation, continuity of care and pregnancy interval was collected from the patients’ medical charts and recorded using Websurvey. Two reviewers looked at each chart and agreed on recorded data.

Results: Data was collected on 125 African American pregnancies: 52 from 1997/1998 and 73 from 2007. While complete data analysis is pending, preliminary results are available. There was no notable increase in continuity of care or pregnancy interval. The results showed some trends which may be related to the drop in African American infant mortality, but did not reach statistical significance. Comparing deliveries in 2007 with those in 1997/1998, fewer women gave birth with less than a high school education (36.5% vs 29.3%; p-value 0.06), fewer had Chlamydia (24.9% vs 12.6%; p-value 0.09) and Gonorrhea (8.5% vs 1.4%; p-value 0.06) during pregnancy and more were breastfeeding at their 6 week postpartum visit (25.0% vs 42.6%; p-value 0.14).
Title: CALCULATING WALL SHEAR STRESS IN THE BASILAR ARTERY OF HEALTHY VOLUNTEERS USING AUTOMATED SPLINE INTERPOLATION AND PC-VIPR, A FAST, RADIAL, UNDERSAMPLED 3-D PC-MRA TECHNIQUE

Authors: Warren Chang, MBA; Andrew Wentland, BS,MS; Steve Kecskemeti, MS; Kevin Johnson, PhD; Yijing Wu, PhD; Charles Mistretta, PhD; Patrick Turski, MD

Department: UW School of Medicine and Public Health, Department of Radiology, Department of Medical Physics.

Mentor: Patrick Turski, MD

Support: Shapiro Summer Research Program and Department of Radiology

Background: Numerous studies have found that wall shear stress (WSS) has prognostic value in determining areas predisposed to atherosclerotic plaque and aneurysm formation1. Acquiring fast, accurate, and non-invasive neurovascular WSS measurements is difficult, but these measurements may have clinical value in the assessment and treatment of neurovascular disorders. Clinically, the basilar artery is a common site for both stenoses and aneurysms, especially in the vertebrobasilar junction and at the basilar tip. We use PC-VIPR2 to generate fast, undersampled 3D-radial whole-brain angiograms and use automated spline interpolation to calculate WSS in the basilar artery of healthy volunteers. Scan time per case is 5 minutes, processing time is approximately 30 minutes.

Methods: 10 volunteers (6 female, 4 male) were scanned using a GE-Health Discovery 750 3.0T MR Scanner and 8-channel head coil using PC-VIPR. Spline interpolation was performed using a MATLAB tool developed in our lab. Postscan, the field of view was narrowed to a 50mm cube surrounding the segment of interest. Points were selected around the basilar artery on complex difference images axial to the vessel to create axial splines from the vertebrobasilar junction to the basilar tip. Using these axial splines as a reference, splines in the anterior/posterior (AP) direction along the basilar artery were created. The intersection of the AP and axial splines created surface points along which an inward unit normal vector was computed; longitudinal WSS was calculated as the viscosity (assumed to be 4.0cP) multiplied by the slope of velocity along the vector. This was repeated for all timesteps in one cardiac cycle. The process is automated such that placing splines defining the vessel of interest is the only input needed to generate a WSS map that can isolate a vessel of interest or show the entire brain.

Results: Time-averaged WSS for all subjects was 0.40±0.08 Pa, consistent with published values for WSS measured with MR.3 We will present localized WSS values for the vertebrobasilar junction, values along the length of the basilar artery, and WSS at the basilar tip.

Conclusion: This study demonstrates that WSS maps can be created from whole-brain highly accelerated 3D PC-VIPR scans. WSS values derived from PC-VIPR velocity data are consistent with values from the literature. While it is well-known that MR underestimates WSS compared to computational fluid dynamics because of lower spatial resolution5, directly measured in vivo values can be used as a surrogate parameter and relative WSS maps of the whole brain can have prognostic value in finding areas predisposed to aneurysm and plaque formation. We are currently creating WSS maps of patients with stenoses and aneurysms and using these normal values as a baseline for comparison with patients.
Title: ZV/ZV' AND ZIIR ELEMENTS OF THE BZLF1 PROMOTER OF EPSTEIN-BARR VIRUS FUNCTION SYNERGISTICALLY TO ESTABLISH AND MAINTAIN LATENCY

Authors: Patrick J. McCarthy, BS; Xianming Yu, PhD; Zhenxun Wang, BS; Hui-Jun Lim, BS; Daniel A. Gorlen; Janet E. Mertz, PhD

Department: Department of Oncology and McArdle Laboratory for Cancer Research, UW School of Medicine and Public Health

Mentor(s): Janet E. Mertz, PhD

Support: Shapiro Summer Research Program, United States Public Health Service grants AI107034, CA22443, and CA14520 from the National Institutes of Health, Pardee Foundation grant, and McArdle Laboratory for Cancer Research

Background: Epstein-Barr virus (EBV) is a ubiquitous gamma herpesvirus that often silently infects its host during childhood or manifests as infectious mononucleosis if infection is delayed until adolescence. Latent infection with EBV has been associated with a number of cancers. Zta, the product of the BZLF1 gene, serves to regulate reactivation of EBV out of latency. We have previously identified two silencer elements of the BZLF1 promoter (Zp), ZV and ZV', which bind ZEB1 and ZEB2/SIP1 to suppress Zp activity. Liu et al. (J. Virol 72:8230, 1998) previously identified another silencer element in Zp, ZIIR. The trans-acting factor that binds ZIIR is still unknown. We have reported that a 2-bp substitution mutation in the ZV element in the context of the B95.8 strain genome leads to spontaneous reactivation out of latency in 293D cells under conditions in which the WT virus maintains latency (Yu et al., PLoS Pathogens. 3(12) e194, 2007). We have recently characterized a 6-bp mutation in the ZIIR element in the context of the viral genome, demonstrating robust lytic reactivation in 293D cells (Yu et al., unpublished data). We have now constructed ZV/ZV' and ZV/ZV'/ZIIR mutant B95.8 strain EBV genomes to determine the interplay between these elements in establishing and maintaining viral latency.

Methods: The mutant B95.8 EBV genomes were isolated as previously described (Delecluse et al., Proc Natl Acad Sci USA. 95:8245-8250, 1998). 293D clones harboring the mutant EBV genomes were isolated and characterized by Western blot, quantitative RT-PCR, Southern blot, and Raji reactivation assay for lytic gene expression, replication of the EBV genome, and virion production. Mutant strain virions were used to infect primary B lymphocytes. Transformation of these cells was quantitatively measured and lymphoblastoid cell lines (LCLs) were isolated.

Results: Characterization of the 293D cell clones infected with these mutant viruses showed spontaneous lytic gene expression and virus production with frequencies as follows: ZV/ZV'/ZIIR mutant > ZIIR mutant > ZV/ZV' mutant > ZV mutant > WT. Upon infection of B lymphocytes, mutant viruses exhibited reduced ability to transform these cells and initiate cellular proliferation. We have begun to characterize LCLs that were isolated after transformation of B lymphocytes with the mutant viruses, with ZIIR mutant LCLs showing robust lytic gene expression. The ZV/ZV'/ZIIR mutant virus, which exhibited a very lytic phenotype in 293D cells, was unable to induce proliferation of sustainable LCLs.

Conclusions: The ZV/ZV' and ZIIR elements function synergistically to maintain EBV latency in 293D cells. Proliferation assays in B lymphocytes suggest that the mutant viruses are defective in inducing cellular proliferation and establishing latency in these cells, the site of latency in vivo. These findings may suggest utility of lytic-induction therapies for associated malignancies which target these silencer elements singly or in combination. Studies in progress include determining the identity of the ZIIR-binding factor, further characterizing isolated LCLs harboring mutant virus, and further investigating the role of these elements during infection of B lymphocytes.
PARATHYROID HORMONE DEFICIENCY AFTER TOTAL THYROIDECTOMY: INCIDENCE AND TIME TO RESOLUTION

Authors: Linda Youngwirth, BS; Joy Benavidez, BS; Rebecca Sippel, MD; Herbert Chen, MD, FACS

Department: Department of Surgery, Section of Endocrine Surgery, University of Wisconsin School of Medicine and Public Health

Mentor: Herbert Chen, MD, FACS

Support: Shapiro Summer Research Program and Department of Surgery

Background: Parathyroid hormone (PTH) deficiency or hypoparathyroidism after total thyroidectomy is not an uncommon post-operative complication. Patients who have PTH deficiency will develop profound hypocalcemia if not properly treated with oral calcium supplementation and activated vitamin D (calcitriol). However, there is little published on the long term outcomes of these patients. The aim of this study was to determine the incidence of PTH deficiency and the time course to resolution after total thyroidectomy.

Methods: We identified 271 consecutive patients who underwent total thyroidectomy from January 2006 to December 2008. All patients had serum PTH levels tested four hours after surgery and the morning after surgery. Patients were diagnosed with PTH deficiency if their serum PTH was <10 pg/mL. The outcomes of patients with PTH deficiency (Group 1) were then compared to patients who did not have PTH deficiency (Group 2). Patients in Group 1 were evaluated for parathyroid function by measuring serum PTH levels as well as documenting usage of supplemental calcium and calcitriol.

Results: Of the 271 patients, 33 (12%) were found to have PTH deficiency. In comparing PTH deficient patients (Group 1) to patients in Group 2, there were no differences in age, gender, thyroid pathology, the incidence of thyroiditis, or other factors which would predict the development of PTH deficiency post-operatively. Of the 33 patients in Group 1, 24 (73%) patients had recovery of their PTH levels to ≥10 pg/mL at their one week follow up appointment while 9 (27%) patients still had PTH levels <10 pg/mL. With long term follow up, 27 (82%) patients had recovered with a PTH level of ≥10 pg/mL while 6 (18%) patients had a serum PTH level <10 pg/mL. However, 3 (9%) required long term calcitriol.

Conclusions: We concluded that approximately 12% of patients undergoing total thyroidectomy will develop PTH deficiency. Of the PTH deficient patients, 73% will return to normal parathyroid function within one week of surgery. Furthermore, 82% of these PTH deficient patients will return to normal parathyroid function with long term follow up. Only 1% of patients undergoing total thyroidectomy will require calcitriol for long-term hypocalcemia.
IMPACT OF TUMOR LOCATION ON MORBIDITY AND MORTALITY: A RETROSPECTIVE FMRI STUDY

Authors: Joel Wood, BS; Bornali Kundu, BS; Amy Utter, BS, MS; Tom Gallagher, MD; Jed Voss, Sirisha Sanamandra, MD; Veena A. Nair, PhD; John S. Kuo, MD; Aaron Field, MD; Chad Moritz, BS; Beth Meyerand, PhD; Vivek Prabhakaran, MD, PhD

Department: Department of Radiology, UW School of Medicine and Public Health

Mentor(s): Vivek Prabhakaran, MD, PhD

Support: Shapiro Summer Research Program and Department of Radiology

Background: Motor and language deficits are particularly debilitating functional deficits and thus a major neurosurgical concern in the preoperative or postoperative setting of brain tumor patients. A critical parameter for predicting deficits is the distance from brain tumor to functioning cortex. We tested the hypothesis that there is an association between distance of tumor lesion to motor cortex (MC) or language areas (Broca’s and Wernicke’s areas) and existence of functional deficits of weakness or aphasia respectively. We also tested for a relationship between these distances and post-operative mortality.

Methods: Our study included patients who underwent either primary or metastatic brain tumor resection at UW-Madison or Madison VA hospital. Preoperative fMRI language and motor maps of 83 and 73 subjects respectively were reviewed retrospectively. The distance parameters were calculated for each subject by finding the minimum distance from tumor to cortical activation. Morbidity information in terms of weakness and aphasia as well as mortality information was examined. Statistical analysis was done using chi-squared test and multivariate ANOVA.

Results: We found a significant association between distance from the tumor to MC and the existence of weakness/paresis (p<0.001), however no significant relationship was found between this distance and mortality (p=0.652). Similarly, a significant association was found between distance of the lesion from either language area and the existence of aphasia (p=0.001) but no significant relationship between this distance and mortality (p=0.857). Moreover, we found a proportional relationship between distance and motor deficit. Incidence of weakness decreases approximately by 30% from less than one centimeter to between one and two centimeters, and then decreases again by approximately 30% for distances greater than two centimeters. This differs from the relationship describing tumor location and aphasia. Here, incidence of aphasia was much higher for distances less than one centimeter and then does not vary beyond this cutoff point.

Conclusions: There was a graded association between decreased distance of tumor from MC and increased incidence of weakness, while there was an asymptotic relationship between decreased distance of tumor from language areas and increased incidence of aphasia. These results may be due to underlying differences in the organization of MC versus language areas. Postoperative mortality was not significantly related to distance of tumor to either motor cortex or language areas.

References:
Title: ACOUSTOELASTOGRAPHY OF THE ACETABULAR LABRUM

Authors: Walker Flannery, BS; Joshua Balts, BS; Hirohito Kobayashi, PhD; James J McCarthy, MD

Department: Department of Orthopedics and Rehabilitation, UW School of Medicine and Public Health; American Family Children’s Hospital

Mentor: James J McCarthy, MD

Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

Background: The hip joint is a ball and socket joint composed of the femoral head and the acetabulum, or hip socket. The acetabulum is surrounded by a circular, fibro-cartilaginous structure called the labrum, which plays a role in joint stability and proprioception. Labral tears are a common medical issue leading to sharp catching pain, popping, and a sensation of locking. Much remains unknown regarding the pathomechanics of labral lesions, and consequently the value of repair. Acoustoelastography is an ultrasound based imaging technique used to assess mechanical properties such as: tissue deformation, stiffness-gradient, and load-bearing capacity in a non-invasive fashion. The aim of our study is to determine the stiffness-gradient of an intact labrum using acoustoelastography techniques and compare these findings to a labral tear model.

Methods: Two intact porcine hemi-pelvises were analyzed. They were prepared by dissecting down to the hip capsule, and planting the femurs in Polyester-Resin with an aluminum casing. The ilium was then positioned on an aluminum plate holder with screws. The hemi-pelvis including aluminum adapter was mounted on the Mechanical Testing System (MTS bionix 858). The MTS machine applied 1Hz (1cycle/sec) sinusoidal displacement to the hip construct. Simultaneously, ultrasound video was captured with a “CINE” image linear probe. A custom design Acoustoelastography analysis (AEA) software program was used to select a region of interest (ROI) from the video. The ROI deformation and echo change were then automatically monitored and a stiffness-gradient was evaluated. Stiffness-gradient within the ROI is depicted as a color spectrum, with red gradient indicating high echo change and stiffness-gradient versus a blue gradient indicating low echo change and stiffness-gradient. Stiffness-gradient and deformation is anticipated to be tissue dependent. All hemi-pelvises were initially tested with an intact labrum in the MTS with AEA. Next, a circumferential incision was made, representing the injury model, and the MTS with AEA was repeated.

Results: Both the intact labrum and labral tear models had similar cyclic echo changes within the ROI, indicating proper MTS setup and labral deformation. The intact labrum and labral tear specimens displayed a mean echo intensity change of 6.5 and 2.5, respectively. The nearly 3-fold reduction in echo magnitude with the labral tear model represents a dramatically decreased stiffness-gradient. This was displayed as a blue-green gradient with AEA.

Conclusions: Initial results show that ultrasound video imaging with AEA is an effective method for assessing the stiffness gradient in our porcine model. Decreased echo displacement among the injury group shows a lower stiffness-gradient, which may reflect decreased function or load-bearing capacity. More trials for data averaging are necessary to reach significant conclusions, but this non-invasive technique may play a prominent role in future research and clinical practice. The study will be continued with an emphasis on increasing statistical power, evaluating other tear modalities, and potentially comparing to labral injury + repair models.
Medical Student Attitudes Regarding Pharmaceutical Companies and Exposure to Their Influence—A 2009 Survey of UWSMPH

Cody Soyk, BS; Branden Pfefferkorn, MD, MPH; Patrick McBride, MD, MPH; Richard Rieselbach, MD

Department of Medicine, UW School of Medicine and Public Health.

Richard Rieselbach, MD

Shapiro Summer Research Program

Medical students represent a group at risk to the influence of pharmaceutical company (PC) marketing. As interactions with the industry come under increasing scrutiny and regulation, previous studies on student-PC relations may no longer be accurate. This study assessed students’ attitudes toward and interactions with PCs at the University of Wisconsin School of Medicine and Public Health (UWSMPH).

A modified questionnaire based on a previously administered national survey was completed by students in April and May, 2009. The survey was analyzed to disclose the frequency of student-PC interactions, where interactions took place, and differences between preclinical and clinical students.

The overall survey response rate was 53.6% (348/649). Most student-PC interactions took place at locations remote from the main campus, with free lunches (70.2%), snacks (66.9%) and small, non-educational items (55.8%) representing the most common gifts. Many clinical students had discussed medical personnel-PC interactions with a physician or friend, and 83.6% of all students believed faculty should be required to disclose industry ties before teaching. Preclinical students expressed greater uncertainty about using PCs as educational resources and were more reluctant to accept PC gifts than clinical students.

Student attitudes toward interactions with PCs reveal the need for further education and guidance regarding these interactions—particularly the risks of using PCs as educational resources. PC exposures remote from the main campus may account for a high proportion of such interactions, which further highlights the need to educate students on conflicts of interest during their preclinical training.
Title: UTILITY OF MICRORNA PROFILE FOR PREDICTING RECURRENCE OF RECTAL CANCER

Authors: Alex Riordan, BA; Marie Stelzer, MD; Tom Warner, MD; Pete Geiger, BS; Gregory Kennedy, MD, PhD

Department: Department of Surgery, Section of Colon and Rectal Surgery, UW School of Medicine and Public Health

Mentor(s): Gregory Kennedy, MD, PhD

Support: Department of Surgery NIH T35 Short Term Training Grant DK 062709-0401

Background: Two basic surgical options exist for early-stage rectal cancer patients: radical surgery and local excision. Radical surgery possesses a low recurrence rate (2-15%), but entails significant morbidity (20-30%). In contrast, local excision has low morbidity, but suffers from an unacceptably high rate of local recurrence (10-40%). Identification of a prognostic marker that could predict recurrence would permit a more accurate assessment of patients’ candidacy for local excision, thereby lowering recurrence rates. Prognostic capabilities have been shown to exist in microRNA (miRNA) profiling. These small, single-stranded RNAs often target oncogenes or tumor suppressor genes and decrease their translation. Specifically, miR-20a, miR-21, miR-106a, miR-181b, and miR-203 were found to be upregulated in colon cancer, and high malignant tissue levels of these miRNAs predicted poor survival. Still, the molecular fingerprint of rectal cancers has never been investigated in relationship to the risk of recurrence. We hypothesized that high miRNA levels in malignant tissue from early-stage rectal cancer patients could predict recurrence after local excision.

Methods: We identified 19 early-stage rectal cancer patients treated with local excision between 1990 and 2005, 6 of whom had recurred. Total RNA was extracted from benign and malignant tissue of formalin-fixed paraffin embedded operative specimens for each patient. Total RNA was then used in RT-PCR and quantitative real-time PCR to probe for miR-20a, miR-21, miR-106a, miR-181b, and miR-203. MiRNA data was evaluated for association with stage of disease and evidence of recurrence collected from the medical record using univariate analysis with Wilcoxon rank sum and Chi square test.

Results: Malignant tissue in both patients who recurred and patients who did not recur had equivalently high levels of miRNA. However, the benign tissue of patients who recurred contained significantly higher levels of all 5 miRNAs when compared to the benign tissue of non-recurrent patients despite having no histological differences.

Conclusions: Based on these findings, we concluded that high miRNA levels of histologically benign tissue obtained from the surgical margin of locally excised rectal cancers can predict recurrence. The malignant miRNA levels did not have predictive value. Further investigation of miRNAs is needed in order to explore their prognostic value and potential to improve patient outcomes.
Title: CHLORIDE COTRANSPORTERS INVOLVED IN THE DEVELOPMENT OF CHRONIC NEUROPATHIC PAIN FOLLOWING SPINAL CORD INJURY

Authors: Tera Hasbargen, BA; Mostafa Ahmed, BA; Gurwattan Miranpuri, PhD; Dandan Sun, PhD; Daniel Resnick, MD

Department: Department of Neurological Surgery, UW School of Medicine and Public Health

Mentor(s): Daniel Resnick, MD; Gurwattan Miranpuri, PhD; Dandan Sun, PhD

Support: Shapiro Summer Research Program and Department of Neurological Surgery

Background: Following a contusion spinal cord injury (cSCI), up to 75% of patients experience debilitating neuropathic pain (NP). Because the molecular and cellular mechanisms for the development of NP are not well understood, it has been difficult to target effective treatments. After SCI, nociceptive genes within the spinal cord exhibit altered expression. Specifically, alterations in Cl⁻ homeostasis affect the function of the GABAergic system and are important in spinal nociceptive processing. GABA function is dependent on the intracellular Cl⁻ homeostasis, which is determined by two major regulatory proteins: inwardly directing Na⁺-K⁺-Cl⁻ cotransporter (NKCC1) and outwardly directing K⁺-Cl⁻ cotransporter (KCC2). Animals showing signs of thermal hyperalgesia (TH) up-regulate NKCC1 receptors and down-regulate KCC2 receptors compared to animals without TH, causing an increase in intracellular Cl⁻ and reversal in both the Cl⁻ equilibrium potential and the normal inhibitory action of GABA. The enzyme(s) involved with NKCC1 phosphorylation and activation has yet to be determined. Understanding the mechanism of NKCC1 phosphorylation may lead to novel treatments for SCI.

Methods: SCI: Following the induction of inhalational anesthesia, a T9 laminectomy was performed and a SCI was created by dropping a 10-g weight from a height of 12.5 mm. The animals were returned to their cages after closing the incision. Locomotor test of SCI animals: The functional neurological deficits were assessed by behavioral analysis using the Basso, Beattie, and Bresnahan (BBB) open-field locomotor test. Animals were observed individually and BBB scores ranging from 0 (no hind limb movement) to 21 (normal movement) was measured before injury (baseline) and on the described post injury days 2, 7, 14, 21, 28, 35 and 42 days. Assessment of TH: TH was used to assess an animal’s ability to withdraw a hindpaw to a thermal noxious stimulus. The rat was placed inside the apparatus and a movable focused beam of radiant heat is placed under the animal’s paw. As soon as the animal moves its paw a photocell turns off the heat, and the latency for the animal to withdraw its paw is recorded. Decreased withdrawal latency time of 3-5 seconds, as compared to baseline values, indicates the development of NP. Hind limb TH testing was performed the day prior to injury and then again on post injury days 21, 28, 35, and 42. Animals were sacrificed and studied 42 days following injury. Immunoblotting: Western blotting is currently being performed to determine the expression of enzymes involved in NKCC1-phosphorylated form in spinal cord tissues. Tissues were homogenized in a lysis buffer containing a mixture of proteinase inhibitors and phosphatase inhibitors and protein concentrations will be determined by BCA protein assay. The resolved proteins will be analyzed. We are using commercially available primary antibodies for enzymes that may phosphorylate NKCC1.

Results and Conclusion: Research is ongoing and immunoblotting is still in process. We anticipate that NKCC1 phosphorylation will increase at each time point following post-injury.
Title: DEVELOPING A TOOL TO EVALUATE STATE PRESCRIPTION MONITORING PROGRAMS

Authors: Callie Hansen, BS; June L. Dahl, PhD; Aaron Gilson, MS, MSSW, PhD; Mary Skemp-Brown, MBA

Department: Department of Pharmacology, UW School of Medicine and Public Health

Mentor(s): June L. Dahl, PhD

Support: Shapiro Summer Research Program, Department of Pharmacology, Wisconsin Pain Initiative

Background: The treatment of pain is one of physicians’ critical duties in the care of patients. However, the diversion opioid analgesics, which are essential for the treatment of pain, may hinder a physician’s willingness and confidence in issuing prescriptions. To resolve this dilemma, states have created policies that track patient, physician, and pharmacist practices regarding the prescribing and dispensing of scheduled medications. However, a wide range of regulations and requirements have been mandated by each state to reduce prescription drug abuse. Our purpose in this study has been to develop criteria to evaluate PMPs, with the intention of identifying ways in which each state can improve in both protecting patient care and privacy and identifying diversion of prescription analgesics. This information would be invaluable to the creation and management of PMP policy.

Methods: A pilot study was conducted to test the criteria for clarity, utility and standardization between states and evaluators. The PMPs in three states- Illinois, Kentucky, and Texas- were evaluated to establish the ability to evaluate state programs with our criteria. State statutes and regulations governing PMPs were evaluated on twelve criteria developed by our team. States were awarded a ‘+1’ for the presence of particular characteristics that protected patient treatment and allowed proper monitoring of diversion trends in the state. States were awarded a ‘-1’ for the presence of certain characteristics that inadequately protected patient care and privacy. The sums the two scores were used to give each state a final score from -13 to +13.

Results: Our criteria gave a range of scores from -7 to +4. Kentucky’s PMP scored +3 with six positive characteristics and three negative characteristics. Illinois’ PMP scored +1 with five positive characteristics and four negative characteristics. Texas’ PMP scored -6 with two positive characteristics and eight negative characteristics.

Conclusions: The criteria developed for this study can be used to evaluate many characteristics of state PMPs. We found a wide range of positive and negative scores which suggests significant differences in the degree to which programs protect patient care and privacy and identify the magnitude of prescription drug diversion and abuse. In the future, we plan to revise criteria to accurately compare the PMPs in a large number of states, and engage several individuals in the scoring process so as to assure the reliability of our comparisons.
ACTIVATION OF SYSTEMIC INFLAMMATORY EVENTS FOLLOWING BRAIN DEATH IN A NON-HUMAN PRIMATE MODEL

Alexander B. Froyshteter, BA; Juan S. Danobeitia, MD; Jamie M. Sperger, PhD; Jolien X. Connor, PhD; Matthew S. Hanson, PhD; Luis A. Fernandez, MD

Department of Surgery, UW School of Medicine and Public Health

Luis A. Fernandez, MD

UW Department of Surgery T35 Short Term Training Grant DK 062709-0401

Brain death (BD) is the primary clinical condition leading to organ donation for transplantation worldwide. BD induces hemodynamic, hormonal, metabolic and immunological alterations associated with severe and irreversible neurological injury but little is known about the molecular changes occurring in the tissues. We have developed a non-human primate (NHP) model for characterization of the initial stages of the multi-systemic cascade of events that are triggered after the induction of BD. We hypothesize that the activation of systemic inflammation leads to oxidative stress that reduces organ quality and thus long-term function after transplant.

Methods: Rhesus and Cynomolgus macaques were used for the NHP model of BD, which was induced by gradual inflation of a balloon catheter placed into the subdural space of anesthetized animals. BD was confirmed by neurologic and angiographic examination. NHPs without induction of BD were used as a control. Tissues were recovered 6 hours after BD induction, kept in cold UW solution and frozen in liquid nitrogen for immunochemistry, Western Blotting, and microarray analysis to compare changes between liver and kidney.

Results: BD NHP animals displayed a hyperdynamic response, diabetes insipidus, and progressive metabolic acidosis. Microarray analysis of liver and kidney mRNA of BD NHP showed a statistically significant upregulation of genes related to the danger-associated molecular pattern proteins (DAMPs) (s100A8, S100A9) and several heat shock proteins relative to control. Additionally, receptors for DAMPs (TLR2 and TLR4) and endothelial cell adhesion molecules (VCAM, ICAM, P-selectin, and L-selectin) were also up-regulated in the liver of BD NHP, but not in the kidney. Furthermore, liver and kidney tissues obtained from BD NHP demonstrated statistically greater infiltration of CD45+ and CD68+ cells. In comparison to controls, pro- (IL1b, TNFa, IL-6 and IFNg) and anti-inflammatory gene (HMOX, COX2 and NOS2a) up-regulation was detected in BD NHP by RT-PCR. Preliminary immunohistochemistry analysis for markers of reactive oxygen species damage (nitrotyrosine, CML) showed an elevation in liver tissue, but not in the kidney of BD animals when compared to control. Compared to control, the liver tissue of BD NHP has elevated levels of SOCS3 protein shown by Western blot as a marker of anti-cytokine activity.

Conclusions: We have observed a characteristic pattern of molecular changes following 6 hours of BD in our NHP model consistent with activation of innate immune responses. The upregulation of DAMPs and inflammatory related genes, and the presence of infiltrating leukocytes following BD, indicates the involvement of the “danger signal pathway”. Further studies will explore if the systemic inflammation in our model had induced significant organ damage to compromise the quality and longevity of the organs post-transplant.
Title: LANGUAGE LATERALIZATION IN BRAIN TUMOR PATIENTS: A RETROSPECTIVE fMRI STUDY

Authors: Amy Utter, BS, MS; Bornali Kundu, BS; Joel Wood, BS; Tom Gallagher, MD; Jed Voss; Sirisha Sanamandra, MD; Veena Nair, PhD; John S. Kuo, MD, PhD; Aaron Field, MD, PhD; Chad Moritz, PhD; Beth Meyerland, PhD; Vivek Prabhakaran, MD, PhD

Department: Department of Radiology, UW School of Medicine and Public Health

Mentor(s): Vivek Prabhakaran, MD, PhD

Support: Shapiro Summer Research Program and Department of Radiology, UW Institute for Clinical and Translational Research (ICTR) grant NIH/UL1RR02501.

Background: Language lateralization (LI) is an essential point of assessment for neurosurgical patients undergoing tumor resection in proximity to the language network. Preoperative fMRI studies of tumor patients have shown activity in both ipsilateral and contralateral homologous areas of the language network. Yet the factors leading to this bilateral activity is unclear. Multiple factors including age, gender, lesion volume, lesion distance to language areas have been linked to LI in various normal and patient populations1,2,3. This study retrospectively explored the relationship of these factors to LI in brain tumor patients.

Methods: Subject information was drawn from a database of consented brain tumor patients who underwent preoperative functional imaging to locate their dominant language hemisphere. 64 right-handed patients were analyzed, 45 male and 16 female, ranging in age from 3-68 years of age, with a mean and std of tumor volume of 37 cc and 42 cc respectively. Threshold of fMRI task activation was set on an individual basis to optimize visualization. LI was used as a measure of how bilateral an individual’s language areas were. This index was determined for Broca’s and Wernicke’s area by measuring area of fMRI task activation in left(L) and right(R) homologous brain regions and calculated using the formula (L-R)/(L+R). Nonparametric statistical methods were employed for data analysis including Wilcoxon-Ranked sum test and Kruskal-Wallis test.

Results: Highly significant relationships were found between decreasing tumor distance to a language area and decreasing LI in that area (Broca’s: p=0.0006, Wernicke’s: p=0.0119). Moreover, there was a significant relationship between decreasing tumor distance to a language area and decreasing LI in other areas of the language network (Tumor distance to Broca’s area v. Wernicke’s area LI (p=0.020); Tumor distance to Wernicke’s area v. Broca’s area LI (p=0.026)). No significant relationships were found between gender, age, or tumor volume and LI.

Conclusions: Decreasing tumor distance to a language area may lead to lower LI in that area or an increase in activity in the contralateral homologous area. It also may have a network effect with less lateralization in other language areas or an increase in activity in other contralateral homologous language areas. Tumor distance to language areas may dominate other putative factors linked to LI. Future studies need to address tumors disrupting neurovascular coupling, affecting BOLD response and measured LI.

Title: PATIENT EXPECTATIONS OF PHYSICIANS CONCERNING COST OF CARE

Authors: Erika L Ruud, MA; Sarah Davis, JD, MPA; Kathleen O’Connell, PhD

Department: Center for Patient Partnerships, UW-Madison

Mentor(s): Sarah Davis, JD, MPA

Support: Shapiro Summer Research Program

Background: In the United States the out-of-pocket cost of healthcare to the patient is the greatest in the world, but health outcomes are some of the worst among developed nations. These mutually insupportable trends make change inevitable, but also speak to the financial burden placed solely on the individual seeking treatment. Physicians make final decisions about the care a patient receives, and therefore participate in deciding the cost to the patient. While there is currently insufficient research on the topic, what exists suggests that both patients and physicians find discussions on the out-of-pocket cost of care important, but engage in them infrequently. To facilitate discourse between health care provider and recipient, and to improve the quality of service to the patient, it would be beneficial to know what patients expect physicians to know and convey concerning the cost of care.

The Center for Patient Partnerships (CPP) at the University of Wisconsin Madison offers free advocacy services to patients facing life-threatening and serious chronic illnesses who specifically seek out their services. Studying the perspectives of these presumably “activated” patients provides an opportunity to explore situations in which patients’ expectations of their physicians were not met, and provide concrete evidence that can guide changes within the system.

Methods: Approximately 20 patients were randomly selected from the CPP database of patients for a phone interview consisting of four predetermined semi-open-ended questions as well as appropriate clarification questions. The interview elicited what the patient believes a physician should know about the cost of the care being provided, and what the physician should communicate during a specific encounter concerning the cost of the encounter as well as other treatments and tests discussed. The interviews were recorded by hand, and the subjects identities were protected. The interviews were coded for themes.

Results: Preliminary analysis of the data suggests most respondents value the physician’s role as an impartial dispenser of diagnoses and treatment. Also, most interviewees believe that true informed consent includes a knowledge of the cost of their care. Some respondents would prefer their physician discuss cost during an encounter; other interviewees would prefer it be another hospital employee.

Conclusions: Further analysis is needed to finalize identification of majority opinions and significant aberrations. Member checks are also required to lend greater validity to this qualitative project before conclusions can be solidified and recommendations to hospitals, physicians, and subsequent researchers can be made.
Title: RESVERATROL INDUCES NOTCH2, SUPPRESSES GROWTH, AND DECREASES NEUROENDOCRINE MARKERS IN MEDULLARY THYROID CANCER

Authors: Matthew Truong, BA; Mackenzie Cook, BA; Scott Pinchot, MD; Muthusamy Kunnimalaiyaan, PhD; Herbert Chen MD, FACS

Department: Department of Surgery, University of Wisconsin

Mentor(s): Herbert Chen, MD, FACS

Support: Department of Surgery T35 Short Term Training Grant DK 062709-0401

Background: Medullary thyroid cancer (MTC) is a neuroendocrine (NE) cancer that frequently metastasizes and is associated with increased levels of hormone secretion and chromogranin A (CgA). Currently, complete surgical resection is the only curative option for MTC. Manipulating signaling pathways may be an effective strategy for the treatment of MTC. The Notch signaling pathway has been validated as a potent tumor suppressor in human MTC cells. Previous work has shown that Resveratrol activates Notch and suppresses NE markers in carcinoid. In this study, we extended our analysis of Resveratrol from carcinoid to MTC, a different type of NE tumor. We hypothesized that Resveratrol could inhibit growth and important NE markers, while inducing Notch signaling in MTC.

Methods: MTC cells treated with varying doses of Resveratrol were assayed for viability using the MTT assay. Western blot analysis for Achaete-Scute Complex-Like 1 (ASCL1), chromogranin A (CgA), full-length and cleaved caspase 3, poly-ADP ribose polymerase (PARP), and active Notch2 Intracellular Domain (N2ICD) was performed. Quantitative real-time PCR (qPCR) was used to measure relative mRNA expression.

Results: Treatment with Resveratrol resulted in growth suppression and an increase in the cleavage of caspase-3 and PARP. A dose-dependent inhibition of ASCL1, a NE transcription factor, was observed at the protein and mRNA levels. Protein levels of CgA, a marker of hormone secretion, were reduced after treatment with Resveratrol. A dose-dependent induction of Notch2 mRNA was observed using qPCR. A dose-dependent increase in N2ICD protein, a marker of Notch pathway activation, was also observed.

Conclusions: Resveratrol suppresses in vitro growth, likely through apoptosis, as demonstrated by cleavage of caspase-3 and PARP. Furthermore, Resveratrol decreased NE markers ASCL1 and chromogranin A. Induction of Notch2 mRNA and N2ICD protein suggests that the Notch2 pathway may be central in the anti-MTC effects observed. Resveratrol is therefore a potential therapeutic option for MTC and future pre-clinical studies are warranted.
Title: TRENDS IN BARIATRIC SURGERY FOR MORBID OBESITY IN WISCONSIN: A SIX YEAR FOLLOW-UP

Authors: Dana S Henkel, MS, P A-C; Patrick L Remington, MD, MPH; Jessica K Athens, MS; Jon C Gould, MD

Department: Department of Surgery, UW School of Medicine and Public Health

Mentor(s): Jon C Gould, MD; Patrick L Remington, MD

Support: Department of Surgery and Department of Population Health Sciences

Background: The prevalence of morbid obesity is increasing throughout Wisconsin and the United States. In 2004, we published a study "Trends in Morbid Obesity and Bariatric Surgery in Wisconsin." We determined that surgery rates were increasing but felt the demand exceeded the capacity of the surgeons. This is a six year follow-up.

Methods: Data was gathered from three sources: the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System, the Wisconsin Hospital Association, and a survey administered to Wisconsin bariatric surgeons.

Results: During 2003-2008, 2.8% of Wisconsin adults were morbidly obese. Although the number of bariatric surgeries performed in Wisconsin remained steady (1,311 surgeries in 2003 and 1,343 in 2008), the types of procedures shifted from open gastric bypass (73% in 2003) to laparoscopic gastric bypass (80% in 2008). The rate of surgery was 1 for every 100 morbidly obese adults. The majority of surgeons surveyed (70%) report insurance benefits as the biggest barrier.

Conclusions: The prevalence of morbid obesity continues to increase in Wisconsin. Bariatric surgery volumes have remained stable but the type of procedure has changed. With only 1% of surgical candidates having bariatric surgery each year, it's likely the needs of this population are not being met.
1. Infection Control Knowledge, Attitudes, and Practices Among Health Care Workers at Mulago Hospital, Kampala, Uganda
   Student: Charles Acher, MPH         Mentor: Ajay K. Sethi, PhD, MHS

2. Multiple Isoforms of Wnk1 Expressed Following Spinal Cord Injury
   Student: Mostafa M. Ahmed, BA       Mentor: Daniel K. Resnick, MD, MS

3. Azacytidine Induces Cell Cycle Arrest and Suppression of Neuroendocrine Markers in Carcinoids
   Student: Vinita M. Alexander, BA    Mentor: Herbert Chen, MD, FACS

4. Attenuating Aging: A Neural Stem Cell Model
   Student: Ruben Alexanian, BS        Mentor: Clive Svendsen, PhD

5. Prevalence of Urinary and Fecal Incontinence in Morbidly Obese Women and Men: The Relationship Between Bariatric Surgery, Incontinence, Weight Loss, and Diet
   Student: Wei An, BS                 Mentor: Erica N. Roberson, MD

6. Characterization of a Tamoxifen-Inducible Cardiac Myosin Binding Protein C Conditional Knock-Out Mouse
   Student: Kerstin E. Austin, BA      Mentor: Richard L. Moss, PhD

7. Newborn Screening in Wisconsin: Should 22q11 Deletion Syndrome be Added?
   Student: Abigail Bales, BS          Mentors: Christina Zaleski, MS
                                            Elizabeth McPherson, MD

8. Are Terminally Threaded Guide Pins From Cannulated Screw Systems Dangerous?
   Student: Joshua Balts, BS            Mentor: James J McCarthy, MD

9. A Family History of Thyroid Cancer Is Associated With More Aggressive Disease
   Student: Joy Benavidez, BS           Mentor: Rebecca S. Sippel, MD

10. The Hygiene Hypothesis: Helminths as a Treatment for Multiple Sclerosis
    Student: Jessica Boland             Mentor: Zsuzsa Fabry, PhD

    Student: Carla J. Bouwkamp, BS      Mentor: Sarina B. Schrager, MD, MS
12. **A Method for Sequential Selective Arterial Catheterization and Digital Subtraction Angiography In Rodents**  
Student: Adam Buhalog, BS  
Mentor: Charles Strother, MD

13. **The Role of Dog Ownership on Immune Development**  
Student: Lillian Chen, BA  
Mentor: James Gern, MD

14. **Coronary CT Angiography to Assist with Percutaneous Coronary Artery Chronic Total Occlusion Recanalization**  
Student: Dhaval Desai, BSE  
Mentors: Nehal Shah, MBBS  
Amish Raval, MD

15. **Accessing the Medical Literature: To Be Affiliated or Not To Be Affiliated**  
Student: Alisha Fahley, BS  
Mentor: Janette Strasburger, MD

16. **Clinicopathologic Categorization of Central Nervous System Malignancies**  
Student: Dave Francis, BS  
Mentors: John S Kuo, MD, PhD  
Shahriar Salamat, MD, PhD  
Kevin Kozak, MD, PhD

17. **Use of Directed Therapy Against the EGF Receptor to Treat Glioblastoma Multiforme Cell Lines**  
Student: Ravindra Ganesh, BS  
Mentor: Paul J Bertics, PhD

18. **Display of Risk and Protective Health Behaviors on Incoming Freshmen Facebook Profiles**  
Student: Kerry Gannon, BS  
Mentor: Megan Moreno, MD, MSEd, MPH

19. **Adherence to Universal Precautions Among Healthcare Workers in Ethiopia: Knowledge, Resources, Application and Personal Behavior**  
Student: Lemlem Getachew  
Mentor: Girma Tefera, MD

20. **Process Improvement in Cystic Fibrosis Newborn Screening**  
Student: Molly Kloosterboer Groose, MS  
Mentors: Philip Farrell, MD, PhD  
Mei Baker, MD

21. **Placental Iron Transporters in Sheep Fetal Growth Retardation**  
Student: Jason M Habeck, BS  
Mentors: Pamela J Kling, MD  
Ronald R Magness, PhD

22. **Retrospective Review of Deep-Brain Stimulator Electrode Therapeutic Impedance**  
Student: Joseph A Hippensteel  
Mentor: Karl Sillay, MD

23. **Balance as a Risk Factor For Pediatric Fractures**  
Student: Ashley Huth, BS  
Mentor: Blaise A. Nemeth, MD, MS
24. **Cure Rates of Superficial Basal Cell Carcinoma Following 1 Versus 3 Cycles of Electrodessication and Curettage: A Randomized Prospective Study**  
   Student: Lydia Kim, BA  
   Mentors: Rosemarie Liu, MD  
   Eric Berg, MD

25. **An Abbreviated Thoracic Onco Geriatric Assessment (Toga) and Its Components Predict Outcomes of Esophagectomies**  
   Student: Anai Kothari, BS  
   Mentor: T. L. Weigel, MD

26. **Assessment of Bone Mineral Density in Female Master Cyclists**  
   Student: Timothy Kufahl, BA, MS  
   Mentor: Alison Brooks, MD, MPH

27. **The Effect of Retinoic Acid on Proliferation of Neural Stem Cells**  
   Student: Rishi R Lall, BS  
   Mentor: Robert J Dempsey, MD

28. **Investigations of the Impact of Microchimerism on T Cell Clones-Specific For Non-Inherited Maternal Antigens**  
   Student: Vu Lam, BS  
   Mentor: William J. Burlingham, PhD

29. **Change In Renal Function and Diastolic Dysfunction Grade Predict Adverse Outcome in Chronic Heart Failure**  
   Student: Adrián Löffler, BSE  
   Mentor: Nancy K. Sweitzer, MD, PhD

30. **The Effect of Shear Stress on Endothelial Nitric Oxide Synthase Activity in Ovine Endothelial Cells: A Preliminary Model**  
   Student: Bianca Manuelli, BS  
   Mentor: Ronald R Magness, PhD

31. **Prevalence, Incidence and Temporal Trends of Kidney Stones in a Rural Wisconsin Population**  
   Student: Ian D. McLaren, BA  
   Mentor: Stephen Y. Nakada, MD

32. **Career Track Experiences of Women Physicians: A Qualitative Study of Life Choices in Medicine**  
   Students: Rebecca McSorley, BS, MSc  
   Mentor: Carol Isaac, PhD, PT  
   Alexandra Schultz, BA

33. **Views of Adolescents on Technologies to Promote and Improve Fitness**  
   Student: Erika J. Mikulec, BS  
   Mentor: Megan A. Moreno, MD, MPH

34. **Methionine Cycle and Insulin Resistance**  
   Student: Appesh Mohandas, BS  
   Mentor Mary Elisabeth Patti, MD

35. **Fighting Cancer Through Improved Governance: Lessons From The U.S. and the European Union**  
   Student: Matt Mokrohisky, BBA  
   Mentor: Thomas R. Oliver, PhD, MHA
36. **Is Rapid Vasodilation in Response to Single Contractions Impaired In Human Obesity?**
   Student: Garrett F Mortensen, BS  
   Mentor: William Schrage, PhD

37. **Validating Aging-Related Brain Mapping Changes in Working Memory Utilizing Acute Stroke Patients**
   Student: Lin Naing, BS  
   Mentor: Vivek Prabhakaran, MD, PhD

38. **Glutamate Immunocytochemical Staining in a Rhesus Macaque With Experimental Glaucoma**
   Student: Hau Nguyen, BS  
   Mentor: T. Michael Nork, MD, MS

39. **Characterization of Two C-Type Lysozymes in the Malaria Vector Anopheles Gambiae**
   Student: Abigail Nitschke, BS  
   Mentor: Susan Paskewitz, PhD

40. **Sorcin Modulation of Na⁺/Ca²⁺ Exchanger Activity in Isolated Cardiomyocytes**
   Student: Mike Oldenburg BS  
   Mentor: Hector Valdivia, MD, PhD

41. **The Role of the Aryl Hydrocarbon Receptor in Transplantation: The Effects of the AHR Activation or Deletion on Skin Graft Survival**
   Student: S. Kyle Pauly BS  
   Mentors: Josh Mezrich, MD  
   John Fechner, MS

42. **MyBPC-Null Mouse Heart Has Increased Basal Energy Requirement**
   Student: Enrique Pena  
   Mentor: J. Carter Ralphe, MD  
   Willem J. DeLange, PhD

43. **Inflammatory Effects of Laryngitis-Associated Pathogens (Helicobacter Pylori, Staphylococcus Aureus and Staphylococcus Epidermidis) on Vocal Fold Fibroblasts**
   Student: Michael Possin, BS  
   Mentor: Susan Thibeault, PhD

44. **Plasmacytoid Dendritic Cell Interferon-α Responses in Children With Asthma and Allergic Sensitization**
   Student: Allison Pratt, BA  
   Mentors: Robert Lemanske, MD  
   Daniel Jackson, MD

45. **Cerebral Oximetry as A Postoperative Marker Following Cardiopulmonary Bypass**
   Student: William Ragalie, BA  
   Mentor: Niloo M. Edwards, MD, FACS

46. **Surgical Outcomes in the Treatment of Pediatric Patients With Slipped Capital Femoral Epiphysis**
   Student: Amrik Ray, BS  
   Mentor: Kenneth Noonan, MD

47. **The Effect of Ascites Fluid And Dcr3 on Tumor Associated Macrophage**
   Student: Beth Read, BBA  
   Mentor: Joseph Connor, MD
48. **Farm to School in Wisconsin**  
Student: Aditi N Ringwala, BS  
Mentors: Amy Meinen, MPH, RD, CD  
Murray Katcher MD, PhD

49. **The Role of the Prefrontal Cortex in “Theory Of Mind”**  
Student: Keisha Rogers, BS  
Mentor: Michael Koenigs, PhD

50. **Maternal Obesity at Delivery: A Risk Factor For Newborn Iron Deficiency**  
Student: Sheila Roy, BA  
Mentor: Pamela Kling, MD

51. **Improving Time and Accuracy of Adipose Tissue Segmentation**  
Student: William Scheels, BS  
Mentor: Scott Reeder MD, PhD

52. **Reducing Infant Mortality Disparities in Wisconsin: Examining the Role of Place in Improving Health Outcomes**  
Student: Shefaali Sharma, BS  
Mentor: Gloria E. Sarto, MD, PhD

53. **Chemotherapy-Based Treatment Improves Survival in Uterine Carcinosarcoma**  
Student: James Spencer, BS  
Mentor: Stephen L. Rose, MD

54. **Biomechanical Comparison Between Two Guided Growth Systems**  
Student: Andrea Stitgen, BS  
Mentor: Ken Noonan, MD

55. **Effect of Child and Parent Factors on Participation in Pediatric Chronic Care Visits**  
Student: Aistis Tumas  
Mentor: Elizabeth D. Cox, MD, PhD

56. **Alzheimer’s Disease: The Effects of Simvastatin on Cerebral Perfusion in At-Risk Individuals**  
Student: Lindsey Vogelman, BS  
Mentor: Cynthia Carlsson, MD, MS

57. **Scoligauge as a Clinical Screening Tool For Scoliosis Patients**  
Student: Mark Welnick, MS  
Mentor: Paul A Anderson, MD

58. **Long-Term Outcome Following Proximal Row Carpectomy For Wrist Arthritis**  
Student: Lucas Wenninger, BS  
Mentor: Jonathan Tueting, MD

59. **Isolation of Multipotent Cardiac Precursor FLK-1+/CD31- Cells From Transgenic Mouse Embryonic Stem Cells**  
Student: Brent E. White, BS  
Mentor: Gary E. Lyons, PhD

60. **Targeting the Mapk Pathway in a Mouse Model of Dilated Cardiomyopathy**  
Student: Alex M Witek, BS  
Mentor: Timothy A Hacker, PhD

61. **Adipose Derived Stem Cells**  
Student: Crystalynn Woodard  
Mentor: Peiman Hematti, MD
62. **Prepregnancy BMI and Nutritional Care Do Not Contribute To Decrease in Dane County’s Black Infant Mortality**
   Student: Carley Zeal, BS
   Mentors: Laura Berghahn, MD
           Gloria E Sarto, MD, PhD

63. **Improving Cardiac Surgical Care: A Work Systems Approach**
   Student: Robert Zemple, MA
   Mentors: Niloo Edwards, MD
           Douglas Wiegmann, PhD

64. **Sexually Transmitted Disease Screening and Improved Birth Outcomes Among African Americans in Dane County**
   Student: Qi Zhang, BS
   Mentor: Gloria Sarto, MD, PhD
           Laura Berghahn, MD
           Murray Katcher, MD

65. **Intensive Insulin Therapy for the Prevention of Infection in the Critically Ill: A Meta-Analysis of Prospective, Randomized Trials**
   Student: Matthew Ziegler
   Mentor: Nasia Safdar, MD, MS
INFECTION CONTROL KNOWLEDGE, ATTITUDES, AND PRACTICES AMONG HEALTH CARE WORKERS AT MULAGO HOSPITAL, KAMPALA, UGANDA

Authors: Charles Acher, MPH; Ajay K. Sethi, PhD, MHS; Bruce Kirenga, MBChB, MMed; Curtis J. Donskey, MD; Achilles Katamba, MBChB, PhD

Department: Department of Population Health Sciences, UW School of Medicine and Public Health

Mentor(s): Ajay K. Sethi, PhD, MHS

Support: Shapiro Summer Research Program and Department of Population Health Sciences Grant

Background: Mulago Hospital is a 1500-bed, national referral hospital in Kampala, Uganda. An infection control team exists, but lack of resources limit its effectiveness. Our objective was to determine the knowledge, attitudes, and practices (KAP) of infection control principles among health care workers (HCWs) in the national referral hospital of Kampala, Uganda.

Methods: We carried out a 66-item, KAP survey of all health care workers including nurses, residents, and attending physicians. Domains included hand hygiene, barrier protection, isolation and contact precautions, and prevention of mosquito-borne transmission of disease. Four-point Likert scales were used to assess knowledge and attitudes (strongly agree, agree, disagree, strongly disagree) and practices (all of the time, most of the time, some of the time, never).

Results: Of the 161 HCWs approached, 146 (91%) completed the survey including 94 (63%) nurses and midwives, 33 (23%) physicians, 14 (10%) nursing or clinical assistants, and 5 (3%) other HCWs. While almost all HCWs (99%) knew to wash their hands between patients, 75% of HCWs disagreed with the fact that their hands, when unclean, were a common way in which infections are spread. The latter varied significantly by occupation (87% for physicians, 77% for nurses, 57% for assistants, 40% for other HCWs; p=0.038). While 98% reported washing their hands to protect themselves from infections, less (81%) did so to protect their patients from infections. Less than half (48%) of HCWs reported having easy access to clean water in between patients. Almost all HCWs (97%) believed that crowded conditions spread infections (97%) but only 60% believed that separating patients with respiratory infections was feasible in their hospital and 61% reported that their ward separated patients with an active respiratory infection from those without. When required, gloves were the most commonly used barrier protection used (95%), followed by masks (61%), gowns (47%), eye protection (34%), and bed nets (26%). Only 60% knew to whom to ask questions regarding infection control and 16% believed their hospital had adequate resources to prevent the spread of infections.

Conclusion: Overall, HCWs had adequate knowledge of infection control principles, although there were some gaps regarding hand hygiene. HCWs at Mulago Hospital in Kampala, Uganda were unable to adequately practice infection control principles due to a lack of time or inconsistent availability of resources.
MULTIPLE ISOFORMS OF WNK1 EXPRESSED FOLLOWING SPINAL CORD INJURY

Mostafa M. Ahmed, BA; Namratta Manhas, PhD; HyunKyung Lee; Kevin King; Gurwattan S. Miranpuri, PhD; Dandan Sun, MD, PhD; Daniel K. Resnick, MD, MS

Department of Neurological Surgery, UW School of Medicine and Public Health

Mentor(s): Daniel K Resnick, MD, MS

Shapiro Summer Research Program, Department of Neurological Surgery, and American Academy of Neurology

Background: Disabling neuropathic pain (NP) following spinal cord injury (SCI) is a significant clinical problem. Chronic neuropathic pain develops in up to 70% of SCI patients. Unfortunately, effective analgesic therapies are not available for treatment of chronic neuropathic pain. The GABAergic system has been implicated in spinal nociceptive processing. Normal GABA function is critically dependent on the activity of the cation chloride cotransporters, Na+-K+-Cl-cotransporter 1 (NKCC1) responsible for Cl- influx and K+-Cl- cotransporter 2 (KCC2) responsible for Cl- efflux. We have previously reported that following a contusion spinal cord injury (cSCI) NKCC1 protein expression is up-regulated and KCC2 expression down-regulated. Moreover, administration of the NKCC1 inhibitor bumetadine (BU) increased the mean hindpaw withdrawal latency time (WLT). These results have implicated the NKCC1 co-transporter in observed decreased WLT following cSCI. However, NKCC1 dependent chloride influx requires the phosphorylation at specific residues. The with-no-lysine(K)–1 (WNK1) kinase has been shown to be an important regulator of NKCC1 phosphorylation in many systems, including nociception. Mutations in a neuronal-specific exon of WNK1 (HSN2) was identified in patients that have hereditary sensory neuropathy type II (HSANII) also implicates WNK1 in nociception, such that these patients have loss of perception to pain, touch and heat.

Methods: Contusive SCI was induced at T9. Animals were evaluated for thermal hyperalgesia (TH) at post-injury days 21, 28, and 42.

Results: Probing for the HSN2 exon of WNK1 reveals two key findings: 1) the HSN2 exon is found in alternatively spliced neuronal isoforms found at 250 kDa and 230 kDa, and 2) the 250 kDa isoform is found only in tissue that is injured.

Conclusions: These data implicate the NKCC1/WNK1 system in post-injury response that contributes the development of neuropathic pain. Targeting this system may have therapeutic benefit.
AZACYTIDINE INDUCES CELL CYCLE ARREST AND SUPPRESSION OF NEUROENDOCRINE MARKERS IN CARCINOIDS

Authors: Vinita M. Alexander BA; Madhuchhanda Roy, MD, PhD; Kristen A. Steffens; Muthusamy Kunnimalaiyaan, PhD; and Herbert Chen, MD, FACS*

Department: Department of Surgery, Division of Endocrine Surgery, UW School of Medicine and Public Health

Mentor(s): Herbert Chen, MD, FACS

Support: Department of Surgery T35 Short Term Training Grant DK 062709-0401 (VMA), NIH – RO1 CA121115 (HC), NIH – RO1 CA109053 (HC), American College of Surgeons: George H. A. Clowes Jr. Memorial Research Career Development Award (HC), Carcinoid Cancer Foundation Research Award (HC)

Background: Neuroendocrine tumors (NETs) hypersecrete neuropeptides that cause debilitating symptoms of carcinoid syndrome, including severe diarrhea, abdominal cramps, and cardiac abnormalities. Surgical resection is the only potentially curative treatment for NETs; however, 90% of NE cancer patients are not candidates for surgery due to extensive hepatic sites involved with the NETs. Recently, DNA methyltransferase inhibitors (DNMTI) such as azacytidine (AzaC) have shown efficacy in clinical treatments of hematological malignancies, but effects on NETs are not well-studied. We hypothesized that this novel class of drugs inhibits NET cell growth and decreases NE markers.

Methods: Three carcinoid types—human midgut (CDNT2.5), pulmonary (H727), and gastrointestinal (BON)—were treated with AzaC (0-100uM) over 6 days. MTT Assays were used to measure cellular proliferation. Western blots were performed with antibodies against chromogranin A (CgA), Neuron-Specific Enolase (NSE), and Cyclin B1. Flow cytometric data was collected from AzaC-treated CDNT2.5 cells for DNA cell cycle analysis.

Results: Treatment of CDNT2.5, H727, and BON carcinoid cells with AzaC resulted in a dose-dependent reduction in tumor cell proliferation. Flow cytometric analysis showed that AzaC-treated cells accumulate in the G2 Phase of cell cycle. AzaC treatment led to: significant decreases in CgA and NSE, indicating that AzaC inhibits neuroendocrine markers; and significant increases in the levels of Cyclin B1, further supporting the flow cytometric data and conclusion that AzaC induces G2/M arrest.

Conclusions: AzaC suppresses cell growth in three different carcinoid types, reduces neuroendocrine markers, and inhibits cell proliferation by inducing G2/M phase arrest. This is the first report that suggests that AzaC suppresses carcinoid cell growth and reduces neuroendocrine markers in vitro. The results suggest that DNMTIs may be a novel class of therapeutic agents that can effectively control tumor growth and the release of bioactive peptides in patients with NETs.
ATTENUATING AGING: A NEURAL STEM CELL MODEL

Ruben Alexanian, BS; Dhruv Sareen, PhD; Clive Svendsen, PhD

Department of Neurology, UW School of Medicine and Public Health

Mentor(s): Clive Svendsen, PhD

Support: Shapiro Summer Research Program and Department of Neurology

Background: The exponential rise in age related diseases in the past century has led to an ever increasing necessity to both understand and combat the pathophysiology of aging. Postulated by Harman in 1956, prolonged exposure to reactive oxygen species (ROS) is one mechanism of aging. A potential model of studying ROS induced aging is through the use of fetal human neural progenitor cells (hNPCs) from Down's Syndrome (DS) patients. DS hNPCs develop and expand normally in the first few population doublings, but subsequently decline in neurogenesis and senesce between 10-15 population doublings. Studies have demonstrated that that the neurodegeneration observed in Down’s syndrome may be partially due to defects in metabolism of ROS and DS neurons exhibit a three- to fourfold increase in intracellular ROS. Mammalian target of rapamycin (mTOR), a serine/threonine protein kinase, is a pathway activated downstream of ROS signaling and is believed to be major regulator of aging. We investigated the role of rapamycin, an inhibitor of mTOR, in increasing the lifespan and neurogenesis of DS hNPCs. However, there are certain limitations to the DS hNPC model, including scarcity of DS cells available for research, slow growth rate, and rapid senescence/death. As such, we generated induced pluripotent stem (iPS) cell lines from the DS hNPCs in order to create a more robust model.

Methods: DS hNPCs and control hNPCs were treated with 100nM rapamycin for 2 weeks and then isolated into single sphere suspensions with continued treatment with rapamycin for another 2 weeks. While in the single sphere suspension, the growth rate of the spheres was analyzed. The same treatment without rapamycin was done for DS hNPCs and control hNPCs for comparison. DS iPS cells were created using episomal vectors as described by Thomson et al. To increase the efficiency of DS iPS cell formation BIO, a Gsk3 inhibitor, and PD98059, an ERK inhibitor, were used.

Results: iPS cell were generated from two DS hNPC lines (K051 and M060). Preliminary data shows that treatment of DS hNPCs with rapamycin for 4 weeks seems to attenuate DS cell senescence and increase growth rate.

Conclusions: Rapamycin can attenuate cell senescence and increase proliferation in DS hNPCs, suggesting that ROS may play an important role in aging in DS neuronal cell population. Moreover, we have generated DS iPS cells that can possibly recapitulate an “aging-in-a-dish” model and provide an unlimited source of DS neural stem cells as a tool for high throughput drug screening. Further studies using neural stem cells derived from DS iPS cells will confirm whether modulating the mTOR pathway can ameliorate the increase in ROS and the rapid aging phenotype.
Title: PREVALENCE OF URINARY AND FECAL INCONTINENCE IN MORBIDLY OBESE WOMEN AND MEN: THE RELATIONSHIP BETWEEN BARIATRIC SURGERY, INCONTINENCE, WEIGHT LOSS, AND DIET

Authors: Wei An, BS; Erica N. Roberson, MD; Arnold Wald, MD

Department: Department of Medicine, Section of Gastroenterology, UW School of Medicine and Public Health

Mentor(s): Erica N. Roberson, MD

Support: Shapiro Summer Research Program and Department of Medicine, Section of Gastroenterology

Background: Obesity is a growing public health concern worldwide because of its increasing prevalence and association with numerous diseases. In addition to increased risk of cardiovascular disease and Type 2 diabetes, research has shown that morbidly obese women are also at high risk for urinary and fecal incontinence. In this case-control study, the prevalence of urinary and fecal incontinence in the obese population in WI will be determined and compared to non-obese controls. In addition, patients undergoing bariatric surgery will be followed before and after surgery to study the effect of bariatric surgery, as well as that of associated factors such as weight loss and diet on urinary and fecal incontinence.

Methods: Obese men and women undergoing bariatric surgery were enrolled in the study prior to surgery. The control populations were non-obese men and women planning to undergo a screening colonoscopy. The Wisconsin Bowel and Bladder Health Questionnaire (WBBHQ) was used to determine both the prevalence and severity of fecal and urinary incontinence.

Results: The target enrollment is 100 at the UW Bariatric Clinic and 14 patients have been enrolled as of 12/2009. Twenty five patients in the control group have completed the WIQ. The two population profiles are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Bariatric</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean BMI</td>
<td>25 ± 5</td>
<td>48 ± 13</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean age</td>
<td>56 ± 6</td>
<td>52 ± 12</td>
<td>0.13</td>
</tr>
<tr>
<td>Gender</td>
<td>79% women</td>
<td>68% women</td>
<td>0.48</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>92% Caucasian</td>
<td>93% Caucasian</td>
<td>0.93</td>
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The prevalence of UI was 50% in the bariatric population compared to 58% in the control group (p = 0.73). The prevalence of FI was 28% in the bariatric population compared to the 20% in the control group (0.64). The fecal severity score was on average 5 ± 4 vs. 3.8 ± 2 (p = 0.18). The urinary severity score were 4 ± 3 and 1.9 ± 1 in experimental and control group. (p = 0.18). No significant differences in UIQ and FIQ (urinary and fecal incontinence quality of life scale) between the two groups were observed.

Conclusions: While a general trend of difference in both fecal and urinary incontinence scores were present, no significant differences were observed. This is most likely due to the low number of enrolled patient. A larger data sample is necessary to generate a significant difference. The most revealing data will follow when incontinence is assessed in the subject population after their bariatric surgery.
CHARACTERIZATION OF A TAMOXIFEN-INDUCIBLE CARDIAC MYOSIN BINDING PROTEIN C CONDITIONAL KNOCK-OUT MOUSE

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Department of Physiology, UW School of Medicine and Public Health

Richard L. Moss, PhD

Shapiro Summer Research Program and UW Cardiovascular Research Center

Background: Cardiac myosin binding protein C (cMyBP-C) mutations are one of the leading causes of familial hypertrophic cardiomyopathy (FHC), which affects approximately 1 in 500 people, and is associated with an increased risk of premature sudden death. However, it is unclear how these mutations lead to the development of clinical disease.

Methods: Given that the majority of cMyBP-C mutations are predicted to encode truncated mutant proteins that are unable to incorporate into the sarcomere, we developed a tamoxifen-inducible cMyBP-C conditional knock-out mouse (cMyBP-C-cKO) to investigate the onset and progression of structural and functional phenotypes due to the loss of cMyBP-C. Temporal and cardiac-specific disruption of cMyBP-C gene expression was achieved by tamoxifen-induced Cre-mediated excision of floxed exons in the cMyBP-C transgene in adult 3-month old mice. Assessment of genetic recombination and protein knock-down was carried out using polymerase chain reaction (PCR) and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) analysis.

Results: Following a seven-day course of tamoxifen injections (80 mg/kg), site-specific recombination of the floxed cMyBP-C transgene was observed in cMyBP-C-cKO myocardium. In addition, SDS-PAGE analysis of myofibrillar proteins isolated from tamoxifen-treated cMyBP-C-cKO myocardium revealed a significant reduction in the level of cMyBP-C expression (∼75% knock-down) at 5 weeks post-injection.

Conclusions: Our findings indicate that tamoxifen treatments are capable of inducing Cre-mediated deletion of the floxed cMyBP-C transgene in cMyBP-C-cKO mice, which in turn leads to a significant reduction in the level of cMyBP-C expression. Future studies will look at the structural and functional consequences of cMyBP-C knock-down to gain further insights into the molecular mechanisms underlying the pathogenesis of cMyBP-C-associated FHC.
Title: NEWBORN SCREENING IN WISCONSIN: SHOULD 22q11 DELETION SYNDROME BE ADDED?

Authors: Abigail Bales, BS; Christina Zaleski, MS; Elizabeth McPherson, MD

Department: Department of Medical Genetics Services, Marshfield Clinic, Marshfield, Wisconsin

Mentor(s): Christina Zaleski, MS; Elizabeth McPherson, MD

Support: Marshfield Clinic Research Foundation Summer Internship and Shapiro Summer Research Program

Background: Advances in genetic technology offer the potential to screen newborns for dozens of additional disorders. Recently, a proposal has been made to add 22q11 deletion syndrome (22qDS), a highly variable genetic syndrome caused by a chromosomal deletion, to Wisconsin’s newborn screen.

Methods: A literature review investigated the incidence, clinical features, and prognosis of 22qDS related to newborn screening. Logistical and ethical issues were considered.

Results: Cardiac defects occur in about 80% of cases and can be life-threatening. However, in all but about 20% of cases, a murmur or cyanosis is present, so only a portion would be saved from an undetectable heart defect. Severe immune deficiency occurs in <1% of cases, but Wisconsin’s newborn screen for severe combined immunodeficiency identifies these infants. Hypocalcemia is common (50-60%), but is often investigated in sick newborns and leads to seizures in only about 20% of affected babies. Treatment may be possible for complications such as failure to thrive and developmental delay, but this benefit does not fit the traditional goals of newborn screening. Screening may prevent a “diagnostic odyssey” for families, though there are concerns about “vulnerable child syndrome” from diagnosis of mildly affected infants.

Conclusions: Though universal screening may prove the incidence to be greater than the estimated 1:5000, the incidence of undetectable life-threatening effects is much less than disease incidence. It is not clear that cardiology evaluation following newborn screening results would be rapid enough to identify severe cardiac anomalies in time for intervention. Additionally, it should be considered if cardiac problems could be more cost-effectively detected by other means, such as pulse oximetry. Addition of 22qDS is likely to set a precedent for other potential syndromes, so changes like adding 22qDS should be considered in the context of more general re-evaluation and revision of Wisconsin’s criteria for newborn screening.
Title: ARE TERMINALLY THREADED GUIDE PINS FROM CANNULATED SCREW SYSTEMS DANGEROUS?

Authors: Joshua Balts, BS; Walker Flannery, BS; James J McCarthy, MD, Kenneth J Noonan, MD; Blaise Nemeth, MD

Department: Department of Orthopedics and Rehabilitation, UW School of Medicine and Public Health; American Family Children’s Hospital

Mentor(s): James J McCarthy, MD

Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

Background: Threaded and smooth pins are often used in orthopedic surgery. Although uncommon, complications such as nerve or vessel injury can occur from aberrant pin placement. Currently there is little data to assess the benefits or risks of threaded versus smooth guide pins. The purpose of this study is to compare the risk of nerve injury from threaded versus smooth guide pins from: 1) past point-drilling of the pin; or 2) entanglement of the pin with soft tissue.

Methods: To test for past point-drilling, a terminally threaded or smooth 1.6 mm guide pin from the 4.5 mm Synthes cannulated screw set (Paoli PA) was randomly selected. A blindfolded participant then drilled until they felt they had passed through the second cortex of a pig femur. The distance drilled past the second cortex was measured in mm. 20 trials were completed, 10 of each pin type.

To test entanglement of soft tissue the terminal portion of the guide pin was placed on a pig nerve. Two drilling positions were tested; drilling at 90° (as if into the table) and parallel to the nerve (drill flat on the table). The drill was run for 1 second and assessed to determine if there was entanglement and if so how much (measured in mm of nerve wrapped by the pin). 60 trials were completed, 15 with each pin type in each of the 2 positions.

Results: The average past point drilling was 4.6 and 16.9 mm for the smooth and threaded pins, respectively (p< 0.05). The second cortex could be identified in all cases with the smooth pin, but only one case with the threaded guide pin. The mean nerve wrapping was 0.45 and 4.7 mm, respectively (p< 0.05) for the smooth and threaded pins drilled at 90° and 0.15 and 0.92 mm respectively (p< 0.05) in the parallel position. In 13 of 60 trials with the smooth pins and 50 of 60 trials with the threaded pins wrapping was noticed (p <.05).

Conclusions: This study demonstrates two things; first, it is difficult to determine by feel when the threaded pin has drilled through the second cortex of the bone compared to the smooth pin and second, soft tissue entanglement is more likely with threaded pins than smooth although it may occur with either.
Title: A FAMILY HISTORY OF THYROID CANCER IS ASSOCIATED WITH MORE AGGRESSIVE DISEASE

Authors: Joy Benavidez, BS; Linda Youngwirth, BS; J Poehls, MD; Herbert Chen, MD FACS; Rebecca S. Sippel, MD

Department: Department of Surgery, UW School of Medicine and Public Health

Mentor(s): Rebecca S. Sippel, MD

Support: Shapiro Summer Research Program and Department of Surgery

Background: Approximately 5% of nonmedullary cancers are familial in origin. A case of familial non-medullary thyroid cancer (FNMTC) is defined as 2 first-degree relatives with thyroid cancer of follicular origin. Most patients that present with a positive family history of thyroid cancer do not meet this definition. The gene responsible for FNMTC has not been identified, and therefore it cannot be used to differentiate FNMTC from sporadic non-medullary thyroid cancer (NMTC). Previous studies have shown that FNMTC may be more aggressive than sporadic thyroid cancer. We sought to determine if patients with a positive family, who may not meet the definition of FNMTC, also display more aggressive disease.

Methods: We conducted a retrospective review of 421 NMTC patients who underwent thyroidectomy from January 1994 to December 2008. We first compared those with a family history of thyroid cancer to those without. Then we compared patients with one affected family member to those who meet the definition of FNMTC (2 or more affected family members). Statistical analysis was performed using SPSS.

Results: 37 (9%) of the patients were found to have a positive family history of thyroid cancer. Patients with a positive family history presented at a similar age and had similar size tumors as patients without a family history. Patients with a positive family history were more likely to demonstrate multi-centricity (41% vs. 22%; p=0.03), malignant lymph nodes (24% vs. 10%; p=0.03), local invasion to surrounding tissues (16% vs. 5%; p=0.02), and had a higher recurrence rate (24% vs. 11%; p = 0.03), compared to those patients without a family history. When we compared patients that met the definition of FNMTC (2 or more affected members) to the patients with only one affected family member there were no significant differences between the groups. Both groups presented with an equally aggressive disease entity compared to the sporadic patients.

Conclusions: Patients with a family history of thyroid cancer present with a more aggressive disease, as demonstrated by an increased rate of multicentricity, lymph nodal involvement, local invasion, and a higher recurrence rate. This was present in all patients with a positive family history, regardless of whether or not they met the definition of FNMTC. Therefore a positive family history should be considered a risk factor for more aggressive disease and this should be taken into consideration when determining the optimal management for these patients.
Title: THE HYGIENE HYPOTHESIS: HELMINTHS AS A TREATMENT FOR MULTIPLE SCLEROSIS

Authors: Jessica Boland; Andrea Isaak, PhD; John Fleming, MD; Zsuzsa Fabry, PhD

Department: UW Department of Pathology and Laboratory Medicine

Mentor(s): Zsuzsa Fabry, PhD

Support: Shapiro Summer Research Program and grants from the National Multiple Sclerosis Society and NIH RO1

Background: The hygiene hypothesis broadly states that immune disregulation may occur due to an immune system lacking sufficient exposure to various antigens in childhood and beyond. Without these influences, the immune system may be improperly activated as in autoimmune disease or allergy and cytokine profiles can reflect a Th1 or Th2 response. Previous work has demonstrated that conditions such as allergy (1) and Inflammatory Bowel Disease (2) can be influenced by the absence or presence of intestinal helminths in humans. Like IBD, multiple sclerosis is a debilitating autoimmune disease for which helminths are being considered as a treatment. Here we report on a preliminary investigation of helminths as a treatment for multiple sclerosis.

Methods: Through the Helminth-Induced Immunomodulatory Therapy (HINT) study, we investigated the possibility that exposure to a foreign organism, the helminth Trichuris suis, might mitigate the immune disregulation associated with multiple sclerosis (MS), a Th1-dominated autoimmune disease. The study, in which five previously untreated MS patients were given a three-month course of live T. suis, focused on ascertaining the safety of helminth therapy in MS patients and additionally allowed investigations of helminths' impact on cells and soluble mediators of the immune system and MS.

Results: While results are preliminary, two patients with active disease on MRI showed both decreased disease activity and a marked trend toward a Th2-skewed immune profile when treatment was applied, an effect which reversed upon cessation of the treatment. Notably, these patients began the study with the most active disease of the study group by MRI and dropped to levels comparable to the other three patients during the course of treatment.

Conclusions: These results are encouraging in that they show a clear effect of helminth treatment on the immune system and an impact on the number of active lesions on MRI in MS patients. This will serve as a basis for our analysis of an upcoming study involving more patients and time points in which we will explore in detail the potential for helminths to influence not only laboratory values, but also the clinical value of helminths as a treatment for MS.


Title: GENDER AND AUTHORSHIP OF PAPERS IN FAMILY MEDICINE JOURNALS 2006-2008

Author: Carla J. Bouwkamp, BS

Department: Department of Family Medicine, UW School of Medicine and Public Health

Mentor: Sarina B. Schrager, MD, MS, Associate Professor (CHS), University of Wisconsin Department of Family Medicine

Support: Summer Student Research and Clinical Assistantship, UW Department of Family Medicine

Background: Despite increasing numbers of women attending medical school and completing residencies, women continue to lag behind men in academic achievement. This lag may be due to women authoring fewer articles since writing articles is an integral part of academic medicine. The aim of this paper is to look at family medicine to see if female authorship is equivalent to that of their male counterparts.

Methods: The five main family medicine journals from 2006 to 2008 were reviewed for gender of lead author and type of article. Gender was confirmed by internet research. Data was entered and analyzed using excel. A current issue of each of the five journals was reviewed to determine the makeup of the editorial boards.

Results: There were 2,126 article reviewed. In total from 2006 to 2008 females authored 33.4% of all articles. In 2006, 32% of the authors were female; in 2007, 34.6% were female; and in 2008 34.1% were female. From 2006 to 2008 33.3% of the authors were female in the JFP; 28.9% were female in the AFP; 36.8% were females in the FMJ; 39.3% were female in the JABFP; and 32.5% were female in the Annals of Family Medicine. The editorial board composition was 27% female in JFP, 50% in FMJ, 25.9% in JABFP, 39.3% in the Annals of Family Medicine, and 10% AFP.

Conclusion: There is a large difference in male and female authorship in family medicine and little has changed over the past three years. There is also a large difference in the composition of the editorial boards of family medicine journals.
Title: A METHOD FOR SEQUENTIAL SELECTIVE ARTERIAL CATHETERIZATION AND DIGITAL SUBTRACTION ANGIOGRAPHY IN RODENTS

Authors: Adam Buhalog, BS; Ryuta Yasuda, MD; Daniel Consigny, BS; Kimberly Maurer, BS; Charles Strother, MD

Department: Department of Radiology, UW School of Medicine and Public Health

Mentor(s): Charles Strother, MD

Support: Shapiro Summer Research Program and Department of Radiology

Background: Using the technique described it is possible to perform sequential serial arterial catheterizations and digital subtraction angiography in rats. This technique will be useful as an adjunct in the use of rodents for the study of human diseases.

Methods: Using a trans-femoral approach 12 adult male Harvey rats were subjected to 3 sequential DSA examinations over a 6-8 week period. At each examination two selective arterial catheterizations were performed, and a DSA acquisition was acquired. Animals were monitored for ill effects, and images from the three examinations were compared for quality and the presence of any arterial injury.

Results: 10 of the 12 rats survived all three examinations. There was no adverse effects noted as the result of the examinations, and there was no evidence of arterial injury.

Conclusions: Using the technique described it is possible to perform sequential serial arterial catheterizations and digital subtraction angiography in rats. This technique will be useful as an adjunct in the use of rodents for the study of human diseases.
Title: THE ROLE OF DOG OWNERSHIP ON IMMUNE DEVELOPMENT

Authors: Lillian Chen, BA; James Gern, MD

Department: Department of Pediatrics, Section of Allergy, Immunology, and Rheumatology, UW School of Medicine and Public Health

Mentor(s): James Gern, MD

Support: Shapiro Summer Research Program and Department of Pediatrics

Background: The increased incidence of allergic disease in industrialized nations led to the proposal that microbial load confers protection against allergy by modulating the development of the immune system ("hygiene hypothesis"). Consistent with this theory, epidemiological studies have shown that children who grow up in homes with pets develop less allergies than those without pets. Elucidating the role of environmental factors such as pet exposure on the immune system can potentially reveal new strategies for allergy prevention. Previous work revealed that dog ownership in infancy is associated with reduced rates of atopic dermatitis and wheeze. Furthermore, dog exposure is associated with enhanced mitogen-stimulated secretion of IL-10, an anti-inflammatory cytokine found to be decreased in atopic individuals. We therefore hypothesized that dog exposure promotes immune tolerance by upregulating production of IL-10, while downregulating production of pro-inflammatory cytokine TNF-α. We also attempted to determine whether the protective effect (if any) correlated with levels of the major dog protein Can f 1 or with bacterial endotoxin normally present in house dust.

Methods: Dust samples from 5 homes with dogs and 5 homes with no pets were extracted and characterized for Can f 1 dog protein and Fel d 1 cat protein using ELISA, while endotoxin was measured using the Limulus amebocyte lysate (LAL) assay. Peripheral blood mononuclear cells (PBMCs) from 10 healthy adults were incubated with the house dust extracts, and IL-10 and TNF-α production were measured with multiplex ELISA. Dog exposure was compared with cytokine responses. In an additional experiment, the cytokine responses were correlated with Can f 1, Fel d 1, and endotoxin levels in the dust. A p-value <0.05 was considered significant.

Results: Subjects exposed to dust from homes with dogs exhibited lower levels of IL-10 than when exposed to homes without any pets, while demonstrating higher levels of TNF-α (p<0.05 in both cases). Furthermore, there was a negative correlation between Can f 1 levels in the dust and IL-10 responses (r= -0.685; p<0.05).

Conclusions: Contrary to expected, dust from homes with dogs induced increased levels of TNF-α and decreased levels of IL-10 relative to dust from homes with no pets in vitro, suggesting that dogs may protect against allergy via a mechanism other than upregulation of IL-10. Recent studies showed that TNF-α from immature dendritic cells (the major antigen presenting cells) may be critical for stimulating IL-10 production by CD4+ T cells, suggesting that although well-known for its pro-inflammatory effects, TNF-α may paradoxically contribute to the development of immune tolerance.
**Background:** Coronary artery disease (CAD) affects millions of people in the United States and around the world. Percutaneous coronary intervention (PCI) of stenotic coronary vessels is quite successful and results in favorable outcomes. However, PCI of coronary artery chronic total occlusions (CTO) remains a major procedural challenge for interventionists. The major obstacle that must be overcome is poor visualization of the occluded artery segment and its trajectory due to poor tissue imaging and lack of contrast in the occlusion with conventional x-ray fluoroscopy. Coronary Computed Tomography Angiography (CCTA) is now being used as pre-procedural planning to assist with PCI of CTOs. CCTA allows for 3D visualization of the coronary architecture, which not only provides the characteristics of the CTO, but also provides a roadmap to the interventionist during the procedure. In spite of a pre-acquired CCTA, certain PCI procedures are still not successful. We hypothesized that features of the CCTA could predict PCI outcome for CTO.

**Methods:** In this retrospective study, patients with CTO were identified using ACC/National Registry Cardiac Catheterization forms. Patients that had a CCTA done prior to PCI attempt of CTO, as a part of pre-procedural planning, were further analyzed. Calcium scores in the coronary tree and the occluded artery were determined using SmartScore application on GE VolumeShare Workstation. The occluded artery was reconstructed in the multiplanar view and a CTO profile map was constructed using this view. A CTO profile score was calculated using this map.

**Results:** There were 9 subjects with CTO who had a pre-PCI CCTA done. One of the subjects’ CCTA had considerable motion artifact and was omitted from analysis. Average CTO lengths were longer in unsuccessful PCI (58 ± 23 mm) vs. successful PCI (26 ± 22 mm; P-value = 0.12). CTOs that had unsuccessful PCI had higher overall and moderately high artery-specific calcium scores (P-values 0.09 and 0.24 respectively). The area under the CTO profile map in the CTO segment was calculated for the intervened CTOs. Successful PCI had, on average, smaller areas under the profile map than unsuccessful PCI (n = 8, P-value = 0.32).

**Conclusion:** In our series, length and calcium scores appear to be reasonable predictors of successful CTO PCI. CCTA appears to be a valuable tool in predicting success rate of CTO recanalization. CTO signal intensity profile may be a better predictor of unsuccessful PCI compared to other indices such as occlusion length and calcium score.
Title: ACCESSING THE MEDICAL LITERATURE: TO BE AFFILIATED OR NOT TO BE AFFILIATED

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Mentor(s): Janette Strasburger, MD

Support: Wisconsin Medical Society Foundation Summer Fellowship in Government and Community Service

Background: Medical literature is a necessity at all stages of research, both in the care of clinical patients and publishing the results of community based research. Although assumed that access to medical literature through the internet is adequate for all researchers affiliated or unaffiliated with a medical school or university, there is little evidence to either support or reject this. Among the most accessible of medical journals to a rural community-based researcher is the state medical society’s monthly journals, and presumably the journal that most newly-established community researchers would use as their first access and publication site.

Methods: This study compared the availability of articles referenced in the first 3 months of this State’s 2009 medical society journal ¹ for an affiliated, university-based researcher and for an unaffiliated rural researcher. Resources at the two in-state medical schools served as a basis for affiliated researcher availability. For an unaffiliated researcher, two publically available search engines – PubMed and Google Scholar – and a state-sponsored search engine ² were assessed. The average cost per article to obtain full text references was also calculated.

Results: An unaffiliated rural researcher had a decreased free full text availability compared to the affiliated, university-based researcher for each of the three search engines examined (state-sponsored search engine 17%, PubMed 35%, Google Scholar 52% vs. Mean Affiliated 86%; P <0.05). Free and low cost resources reduced but did not eliminate this disparity. Using the best options available, the average price to obtain full text references presuming the researcher would be writing an article exceeded $250 using publishers or document suppliers, and exceeded $90 using the state medical school library.

Conclusions: Access to full text medical literature for unaffiliated researchers is present only at substantial personal cost, and this may represent a barrier to rural research. Cooperation through medical libraries, publishers, foundations, and community arms of federally-funded translational research initiatives may open greater access for rural researchers.

² BadgerLink (Ebsco search engine) a project of the Wisconsin Department of Public Instruction, Division for Libraries, Technology and Community Learning
Background: Glioblastoma multiforme (GBM), or WHO grade IV astrocytoma, is the most aggressive primary brain tumor in humans. The pathogenetic mechanisms of gliomagenesis remain poorly defined. Two classifications for GBMs exist: primary and secondary. Primary GBM tumors manifest de novo while secondary tumors typically develop through malignant progression from lower grade astrocytomas. Current therapies including maximal surgical resection, radiation therapy, and chemotherapy only prolong median survival to approximately 14 months. A more detailed understanding of new mechanisms involved in GBM tumorigenesis will lead to better diagnosis, staging, and treatment. Tissue microarray analysis will speed discovery of molecular markers in GBM’s and other brain tumors, potentially improving outcome. Tissue microarrays consist of paraffin blocks in which up to 1000 separate tissue cores are assembled into an array block to permit high throughput analysis of many different specimens. A hollow needle is used to remove tissue cores from the pre-screened regions of paraffin embedded tumor samples. These cores are then inserted in the tissue microarray paraffin block in a precise pattern. Sections from this microarray block are then prepared for immunohistochemistry or fluorescent in situ hybridization to investigate the differential expression of proteins/genes of interest in a large number of GBMs. These analyses are coupled with clinical outcome data to potentially develop tumor biomarkers for diagnostic and therapeutic strategies.

Methods: 208 Grade IV Astrocytoma tissue samples were selected from the UW Clinics neuropathology archives from 1997 to December 208. Additionally, 5 Grade III Astrocytoma samples, 5 Grade II Astrocytoma samples, 5 Grade II Oligodendroglioma samples, 5 Meningioma samples, and 5 Hippocampus/Neocortex samples were selected. Overall, 233 samples and 564 cores were assembled into 3 tissue microarray blocks. A clinical database is currently being developed with meticulous clinical annotation of specimens used in the microarray with the goal being to discover potentially involved molecular markers. Data collected include age, gender, Kaposi performance status, symptoms, pathologic diagnosis, resection date and type, therapy (adjuvant radiation, concurrent chemotherapy, adjuvant chemotherapy), recurrence/progression date and therapy, date of death, WBC count, hematocrit count, platelet count, Hemoglobin count.

Results: IRB approval obtained. Three Grade IV Astrocytoma Tissue Microarrays with control samples have been constructed. Clinical database development is ongoing.

Conclusions: Future directions of the study include completing the clinical database and beginning testing cell surface adhesion markers on the microarrays. Data from IHC testing will then be compared with the clinical database in the hopes of identifying potential tumorigenesis markers as well as better understanding Grade IV Astrocytoma pathogenesis.
Title: USE OF DIRECTED THERAPY AGAINST THE EGF RECEPTOR TO TREAT GLIOBLASTOMA MULTIFORME CELL LINES

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Department: Department of Biomolecular Chemistry, UW School of Medicine and Public Health

Mentor: Paul J Bertics, PhD

Support: Shapiro Summer Research Program and Department of Biomolecular Chemistry

Background: The theory of oncogene addiction states that tumor cells which have mutated extensively may have parts of their cellular machinery significantly upregulated, and in fact, the cell's survival may depend solely on these upregulated pathways. Directed therapy against specific molecules in these upregulated pathways would be highly effective against specific cancers and relatively non-toxic to the remainder of cells in the host, and thus highly desirable. We studied two glioblastoma multiforme cell lines, one of which (U87) expressed predominantly wild type EGF receptors on its surface, and the other (A172) expressed a mutant EGF receptor (TKD mutation) along with the wild type EGF receptor. We were investigating to see if the A172 mutation was oncogene addicted, and hence more sensitive to EGF receptor directed therapy - two small molecule inhibitors (erlotinib and gefitinib), and a monoclonal antibody against the EGF receptor (cetuximab).

Methods: The two glioblastoma multiforme cell lines were grown using standard tissue culture methods. 48-well plates were created with each cell line and exposed to one of 6 conditions - HEPES only, DMSO (1 J.lM in HEPES), Gefitinib (0.1 J.lM in HEPES), Erlotinib (1 J.lM in HEPES), Cetuximab (20 J.lM in HEPES), and a blank column for control. After one day, the first four rows had their normal serum changed, and the second four rows were serum starved. On days 2, 3 and 4, each column was treated with the appropriate drug, and cell bioactivity was measured using MTS assay on Days 2, 3, 4 & 5.

Results: We showed that the two cell lines were both killed by the directed therapy against the EGF receptor, but expressed differential sensitivity to the chemotherapeutic agents being used. Cell line U87 was equally sensitive to all three drugs, while the A172 cell line was more sensitive to cetuximab than gefitinib, and least sensitive to erlotinib.

Conclusions: The two cell lines expressing differential sensitivities to directed therapy against the EGF receptor is indicative of a role for genetic typing of glioblastoma tumors in order to select the best targeted therapy for them. Knowledge of the differential sensitivities of different tumor cells, and the cell type involved in the tumor being treated has great potential for the genesis of highly selective chemotherapy with minimal side effects.
Title: DISPLAY OF RISK AND PROTECTIVE HEALTH BEHAVIORS ON INCOMING FRESHMEN FACEBOOK PROFILES

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Mentor(s): Megan Moreno, MD, MSEd, MPH

Support: Shapiro Summer Research Program and Department of Pediatrics

Background: Adolescent health providers frequently assess an adolescent’s balance of health risk behaviors (such as alcohol use), and protective behaviors (such as sports involvement). The purpose of this study was to perform a content analysis on Facebook profiles to explore associations between adolescents’ displayed risk and protective behaviors.

Methods: This study analyzed publically accessible Facebook profiles of 18 and 19 year old incoming University of Wisconsin freshmen. Profiles were analyzed for displays of risk behaviors including sex, alcohol, tobacco, drugs, and hookah; for protective behaviors including sports, the arts (drama, dance, and music), and religion; and for any references to personal health including chronic illness, mental illness, weight concerns and sleep problems.

Results: Of the 222 evaluated profiles, a content analysis was performed on the 100 profiles that met inclusion criteria. Of these profiles, 97% were 18 years old and 54% were female. One or more risk behaviors were present on 74% of profiles, one or more protective factors were present on 70% of profiles. There was no overall association between the display of risk and protective behaviors. There was a positive association between being female and displaying references to weight (p=0.05). In addition, there was a positive association between male gender and the display of references to sports (p=0.03). There was also a positive association between the display of references to the arts and sleep (p=0.04).

Conclusions: Facebook provides an innovative way to explore the balance between displayed risk and protective behaviors among adolescents. Given the high prevalence of both displayed risk and protective behaviors, adolescents appear to use Facebook as a place to display many types of behaviors. The display of references to personal health is far less common. The significant gender differences in the display of weight by females and sports by males follows gender patterns seen in other studies. The relationship between display of references to art and sleep provides an interesting association that should be further investigated. Further studies should evaluate how risk and protective behavior displays change as students progress through college.
Title: ADHERENCE TO UNIVERSAL PRECAUTIONS AMONG HEALTHCARE WORKERS IN ETHIOPIA

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Mentor(s): Girma Tefera, MD

Support: Shapiro Summer Research Program and Department of Surgery

Background: Blood-borne pathogens have long been recognized as occupational hazard to healthcare workers.1-5, 8-10 Exposure to blood and other body fluids are the major risk factors for occupational acquisition of blood-borne infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).1-5 Universal precaution (UP) remains the cornerstone of protecting healthcare workers (HCWs) from infection with blood-borne pathogens. A recent study investigated the attitude of health care workers toward UPs in two regions of eastern Ethiopia and found that adherence of healthcare workers to UPs to be suboptimal.1 The aim of the current study is to explore factors that might contribute to compliance/noncompliance to universal precautions among healthcare workers in Addis Ababa, the capital city of Ethiopia.

Methods: The study was conducted in two major hospitals: Black Lion and St. Paul Hospitals. The study subjects included doctors (N = 76), surgeons (N = 37), nurses (N=125), medical students (N = 95), laboratory technicians (N = 49), and janitors (N = 103). Data was collected using self-administered and structured confidential questionnaires. Total of 600 questionnaires were distributed and data was collected using self-administered and structured confidential questionnaires. The data was analyzed using Stata statistical analysis software. Logistic regression models were used to assess statistical significance.

Results: Response rate was 83% (497/600). 485 questionnaires were entered for data analysis. Analysis of knowledge of UPs assessed by how often hands were washed after each patient contact is relatively suboptimal among doctors (52%) and surgeons (58%) and Janitors (39%). Only 38% doctors, 34% surgeons, 28% medical students, and 53 % janitors reported that UP guidelines are included in their job/educational training. Needlestick injuries are underreported among surgeons (26%), doctors (28%), janitors(32%), laboratory technicians (38%) Application of UPs is substandard among doctors (46%), surgeons (59%), medical students (49%), and janitors (57%). Only 31% of janitors, 42% of doctors, and 59% of medical students reported that there are adequate equipments/resources to enable application of UPs. Application of UPs is strongly associated with UP training (OR: 2.18; 95% CI: 1.25-3.81; P: 0.006) and the knowledge of the importance of washing hands after each patient contact (OR: 4.38; 95% CI: 2.45 – 7.82; P: 0.000). Preventing Needlestick injury is strongly associated with avoidance of needle recapping (OR: 0.470; 95% CI: 0.261-0.845; P: 0.012). Furthermore, the study showed medical students are more likely to avoid needlestick injury (OR: 0.117; 95% CI: 0.031-0.445; P: 0.002) because they are less likely to recap used needles (OR: 17.38; 95% CI: 3.716; P: 0.000). They are also more likely to report needlestick injury (OR: 8.97; 95% CI: 2.35 – 34.20; P: 0.001).

Conclusions: In conclusions knowledge and application of UPs among healthcare workers of Ethiopia is unsatisfactory. The findings showed that knowledge/adequate training of UPs plays a crucial role in how well HCWs practice universal precautions in healthcare setting. Therefore, there is a need to incorporate UP guidelines into the medial education/job training of HCWs in Ethiopia. In addition, practice of universal precautions should not be left to the discretion of HCWs and should be mandatory. This should be supplemented by supervision, adequate health care supplies, and clear guideline in the prevention of exposures to blood and other body fluids.
Title: PROCESS IMPROVEMENT IN CYSTIC FIBROSIS NEWBORN SCREENING

Authors: Molly Kloosterboer Groose, MS; Richard Reynolds, MSIE, MHA; Zhanhai Li, PhD; Mei Baker, MD; Philip Farrell, MD, PhD

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Mentor(s): Philip Farrell, MD, PhD; Mei Baker, MD

Support: Shapiro Summer Research Program and Dr. Farrell’s Turrell Professorship funds

Background: After early diagnosis of cystic fibrosis (CF) through newborn screening (NBS) was recommended by CDC in 2004, an unprecedented rate of worldwide implementation ensued using analyses of immunoreactive trypsinogen (IRT) and DNA. With such a rapid change and the recognition of implementation difficulties, quality improvement (QI) has become essential. With this in mind, we undertook a multi-phased QI project. In the first phase, we worked with collaborators from three NBS programs in the United States to adapt and perform QI exercises using the Process Failure Modes and Effects Analysis (PFMEA) method. In another phase, we analyzed IRT and DNA data from Wisconsin’s CF NBS program at the Wisconsin State Laboratory of Hygiene (WSLH).

Methods: The PFMEA study revealed that false negative NBS results were a major concern, so we have subsequently concentrated on that issue. The WSLH maintains three databases regarding CF NBS: one of laboratory screening results, one of sweat test results of infants screening positive (i.e., IRT ≥ 96th percentile and 1 or 2 CFTR mutations detected), and one of false negatives (i.e., children with CF that are diagnosed based on signs and symptoms after a negative IRT/DNA screen). Using these three databases, we analyzed the efficacy of Wisconsin’s use of the ACMG panel of 23 DNA mutations (∆F508 and 22 less common alleles) and determined if the infant’s false negative status was due to the IRT or DNA portion of the screening protocol. We also looked for evidence of missed minority babies due to non-ACMG panel mutations.

Results: At the beginning of data analysis, we discovered a significant amount of data was missing from the WSLH database regarding infants with borderline sweat test results. We then began contacting CF centers around the state to obtain the missing information. Analysis of the false negative database proved insightful. Between 1994 and 2006, there were 8 false negatives with 5 due to low IRT levels and 3 due to mutations other than ∆F508 mutations that were not covered in the screening protocol at that time. None of the false negatives were minorities.

Conclusions: The DNA step of the screening protocol is not the main cause of false negative CF NBS results in Wisconsin. There were no false negative minority babies in the 12 year period indicating the ACMG panel of mutations is currently sufficient for the Wisconsin population. We hope to gain further insight into how changes in the screening protocol could potentially affect the sensitivity and specificity after completion of the DNA database analyses. Upon integration of all of our QI efforts, we will improve CF NBS by making it as efficacious and equitable as possible for all infants screened in the United States.
Background: Placental to fetal iron transport is impaired in growth retarded fetuses, resulting in low tissue iron levels. Our lab utilizes a sheep uterine restriction model to study the effects of insufficient gestational space on placental and fetal development. Sheep and human placentae differ in cellular alignment, with a single trophoblast layer in human, but fetal and maternal trophoblast layers in sheep. It is known that cell surface transferrin receptor (TfR) is likely involved in human placental iron transport, but it is not known if TfR is involved in sheep placental iron transport. Hypothesis: TfR expression will increase in IUGR models due to the overcompensation of TfR transcription in response to low iron stores.

Methods: To promote uterine restriction, ewes underwent a single uterine horn ligation under anesthesia 2 months prior to conception. Singletons, twins and triplets were delivered at 120 or 130 days gestation (term=145) under anesthesia. Placental weight, placentome number and types were recorded as well as fetal numbers/pregnancy. Placentomes were fixed in formalin, paraffin-blocked and tissues stained in H&E, Gomori Trichrome (collagen I) and Perl’s Prussian Blue. Additional tissues underwent antigen extraction and were stained for human CD-71 TfR. Digital photomicrographs were taken.

Results: Microscopic placentome structures (vessels, microvessels, myometrium, endometrial glands, fetomaternal interface, and fetal chorion) were seen. Prussian blue iron stain showed minimal staining, except for small sites of intense staining in a subchorial distribution described as the hemophagic zone. Trichrome staining (collagen I) was seen mostly in blood vessel wall supporting structure. In the IUGR group, additional collagen staining was seen outside the vasculature that could indicate tissue scar. Placentomes showed specific TfR cell binding on intercotyledonary trophoblasts, endometrial gland cells, vascular endothelium, vascular smooth muscle cells, trophoblast cells at villus junction, as well as on Hofbauer cells, with strongest staining on the intercotyledonary trophoblasts and weaker staining on the villus trophoblast cells. Growth restricted placentae exhibited stronger staining of villus trophoblasts, endothelial, vascular smooth muscle and vascular support stroma, compared to the controls.

Conclusions: Placental structure and histology was recognizable in tissues. Human TfR antibody binds specifically to sheep placenta. Greater collagen and TfR staining was observed in growth-retarded placentae compared to control placentae. We speculate that TfR is involved in fetal iron transport in the sheep and also that TfR is upregulated in growth retardation. Further work is needed.
Title: RETROSPECTIVE REVIEW OF DEEP-BRAIN STIMULATOR ELECTRODE THERAPEUTIC IMPEDANCE

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Mentor(s): Karl Sillay, MD

Support: Shapiro Summer Research Program and Department of Neurological Surgery

Background: Deep-brain stimulation is becoming a common therapy for a variety of neurological disorders ranging from Parkinson’s Disease to Obsessive Compulsive Disorder. Until recently, most stimulation devices have functioned as constant-voltage devices. Newer devices are now available that allow for current-controlled stimulation, theoretically allowing for the delivery of the same current density to the tissue regardless of inflammation and electrode characteristic changes. This constant-current density is used under the premise that electrical impedance, or the resistance to current flow, is changing with time. Transient changes in impedance with electrophysiology microelectrode devices and model deep brain stimulation electrodes have been observed, but there has been no methodical, clinically-relevant evaluation of deep brain stimulation electrode characteristics.

Methods: A retrospective review of 9 years of patient records was conducted, specific to deep brain stimulator implantation with Soletra impulse generators. A total of 89 patients and 171 electrodes were reviewed. All data was collected in Microsoft Excel (Redmond, WA) and analyzed using Matlab (Natwick, MA). Only data from patients whose stimulation settings were not changed for a minimum of 3 consecutive visits were included in the final analysis. A total of 1009 data points over a period of 4019 days post-implant were extracted from the original data set for final analysis.

Results: No significant differences in impedance were observed for all electrodes when binned over 90 day periods. Binned data was then compared when the case was used as the anode (monopolar) and no significant changes in impedance were observed. Significant differences (p < .01) were seen in impedances when the impulse generator case was not used as the anode (bipolar). This was particularly prominent over the first 90 days compared to many subsequent time periods.

Conclusions: The results of this study suggest that voltage controlled devices or settings may be sufficient for periods beyond the first 90 days of deep brain stimulator implantation when bipolar stimulation is used. Voltage controlled stimulation may be adequate throughout the lifetime of the patient when monopolar settings are used. This could allow for extended battery life and potentially obviate the shift toward current-controlled devices or settings.
Title: BALANCE AS A RISK FACTOR FOR PEDIATRIC FRACTURES

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Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

Background: Fractures are the fourth most common emergency department primary diagnosis for 13-21 year olds and account for approximately 30% of pediatric orthopedic office visits (CDC, NCHS). Within this population studies have shown that certain individuals may be at an even a greater risk for balance-related fractures, namely those who are either under and overweight (Hue 07). The increased rate of fracture may be due to the combination of impaired balance with either decreased bone mineral density or increased loading on the musculoskeletal system, respectively. While risk factors and the role of balance has been extensively studied in other high-risk populations such as the elderly, risk factors and impaired balance not been as widely studied in the pediatrics (Runge 05). Current studies that look at the relationship between balance and fracture risk in pediatrics typically utilize expensive and time consuming tests to find a correlation (Ma05, Goulding03). While this method is sufficient for research, an inexpensive, clinically applicable alternative is desired to identify at risk individuals. The purpose of this study will be to select an appropriate test and find cut-offs that can help identify at risk individuals with impaired balance whom preventative balance training could be indicated, if a relationship between balance and fracture risk is found. Moreover, adjusted cut-offs for high-risk populations may also be determined.

Methods: A cross-sectional case-control observational study of coordination in upper extremity fracture cases as compared to GI controls was conducted. Data for 100 cases and 35 controls was obtained. Each subject performed three balance exercises three times each, including an eyes-closed static, and eyes-open and eyes-closed dynamic tests. Static tests were performed on the floor where as dynamic tests were performed on an Airex Balance Pad. A ceiling limit of 180 seconds was allowed for each exercise, and the best performance time on each exercise was used for data analysis.

Results: Preliminary data showed no statistical difference between balance times for fracture and non-fracture patients in any of the exercises. However, eyes-closed static and eyes-open dynamic tests showed the greatest variation between fracture and non-fracture patients. BMI z-score balance times showed a trend with lowest balance times at the extremes of the BMI z-scores. Balances times also varied with age, with youngest and oldest patients having the shortest and longest balance times, respectively.

Conclusions: The eyes-closed dynamic exercise is an insufficient test to identify individuals whom preventative balance training is indicated. However, additional data is needed for both non-fracture patients and patients with BMI z-scores on both extremes to select the best test and corresponding cut-off times to indicate preventative balance training. These cut-off times may also be stratified by age and gender.
Title: CURE RATES OF SUPERFICIAL BASAL CELL CARCINOMA FOLLOWING 1 VERSUS 3 CYCLES OF ELECTRODESSICATION AND CURETTAGE: A RANDOMIZED PROSPECTIVE STUDY

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Mentor(s): Rosemarie Liu, MD; Eric Berg, MD

Support: Shapiro Summer Research Program, the Skin Cancer Foundation, and UW Carbone Cancer Center

Background: Basal cell carcinoma (BCC) is the most common form of skin cancer in the United States, with over 900,000 new cases in the U.S. every year. Electrodessication and curettage (ED&C) is a commonly performed procedure in the outpatient dermatology setting to treat BCCs. To perform ED&C, a curette is used to debulk the tumor. The curetted site is then burned with an electric needle to destroy any residual tumor cells. This constitutes one cycle of ED&C. The optimal number of ED&C cycles required to achieve an adequate cure rate has been controversial. Currently, it is standard clinical practice to perform three cycles of ED&C, but this may result in greater tissue destruction and greater morbidity than with one cycle of ED&C. There have not been well designed evidence-based studies supporting the advantages of performing three cycles versus one cycle. The primary goal of the study is to determine whether there is a difference in cure rates of superficial BCC following one cycle of ED&C versus three cycles of ED&C.

Methods: Subjects meeting eligibility criteria are randomly divided into one of two treatment groups (ED&C x 1 cycle or ED&C x 3 cycles) using computer generated random numbers. One cycle of ED&C is defined according to standard technique currently employed. It involves scraping away the tumor with a curette and then burning the curetted site with a small electric needle (electrodessication). During Visit 1, the surgical site is marked, local numbing medication is injected, and 1 or 3 cycles of ED&C is/are performed. The site is photographed pre- and post-operatively. All four follow-up visits (3, 6, 9, and 12 months after Visit 1) include skin evaluations by the physician who performed the ED&C. The lesion site is examined, measured, and photographed for clinical evidence of recurrence, as defined by a new lesion within the previously treated site. If there is evidence of possible tumor recurrence at the treated surgical site during Visit 2, 3, 4 or 5, then the lesion will be biopsied using a shave procedure. The targeted patient recruitment is 140.

Results: Of the 42 study patients who have been recruited thus far, 19 have completed all 5 study visits and none had clinical evidence of recurrence. No serious adverse events related to the ED&C procedure have been reported to date. Patient recruitment and data collection is ongoing.

Conclusions: A goal of the study is to improve patient care by treating subjects with a less invasive surgical procedure (ED&C x 1 cycle) than the current standard of treatment (ED&C x 3 cycles), while achieving equal cure of their BCC. If ED&C x 1 is at least equivalent to ED&C x 3, patients treated with ED&C x 1 could potentially have faster healing times of their surgical sites, better cosmetic outcomes, and experience fewer post-surgical complications. The study is ongoing with anticipated completion in 2010.
Title: AN ABBREVIATED THORACIC ONCO GERIATRIC ASSESSMENT (TOGA) AND ITS COMPONENTS PREDICT OUTCOMES OF ESOPHAGECTOMIES

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Mentor(s): T. L. Weigel, MD

Support: Shapiro Summer Research Program and Department of Surgery

Background: Surgical resection is a high risk, potentially curative, therapeutic approach used to treat esophageal cancer. At present, no tool currently exists to easily allow surgeons to objectively quantify surgical risk in geriatric patients undergoing major thoracic surgeries. The goal of our study is to develop a pre-operative thoracic onco-geriatric assessment (TOGA) which is patient and physician-friendly, and successfully estimates surgical risk in geriatric patients presenting with primary esophageal carcinoma.

Methods: Patients ≥70 years old were recruited to participate in a prospective, IRB-approved study that involves the preoperative administration of a panel of validated functional and cognitive screening tests including: Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Geriatric Depression Screen (GDS), Brief Fatigue Inventory (BFI), Eastern Cooperative Oncology Group Performance Status (ECOG PS), Mini Mental State Exam (MMSE), and a Mini Nutritional Assessment (MNA).

Results: Interim analysis was performed on 19 patients over the age of 70, who had an esophagectomy between August, 2007 and February, 2009. The overall and thirty day mortality was 0% (0/19) and 0% (0/19), respectively. ECOG PS score predicted patient discharge to a nursing home (CC* = .51 p = .02). Both the MNA score (CC = .44 p=.06) and BFI score (CC = .43 p =.06) correlated with post-operative complications. The MNA score was also marginally predictive of the odds of an extended length of stay (OR* = 11.19 p = .10). *CC = correlation coefficient, OR = odds ratio.

Conclusions: Our initial data suggest that an abbreviated TOGA including three simple screening tests: MNA, BFI, and ECOG PS could be used as a pre-operative risk stratification tool for geriatric patients with esophageal cancers undergoing esophagectomy. Ongoing study may validate these preliminary results and will hopefully yield an abbreviated TOGA assessment to improve utility. These outcome data may enable geriatric patients and their physicians to make more informed treatment choices.
Background: Low bone mineral density (BMD), or osteoporosis, is a serious health problem because of its association with life-debilitating and costly fractures. Previous research in male subjects has shown that greater amounts of activity in non weight-bearing activities like cycling correlate with poor bone health. While the vast majority of these experiments have been in male subjects, osteoporosis prevalence is greater than 3:1 in women compared to men. Because of this, exercise interventions that promote bone health in this population are of particular importance. The objective of this experiment is to assess and compare the BMD of the hip and lumbar spine in competitive female master cyclists to that of normally active female controls.

Methods: Cross-sectional observation study, stratified by age group. Subjects include 56 total female subjects, ages 35-55; 28 competitive female master cyclists (consistent participation in year-round cycling training for a minimum of 6 hours or 60 miles per week for a minimum of 2 years and compete in competitive cycling events and are engaged in little to no weight-bearing exercise) and 28 controls (participation in 30 minutes of moderate or vigorous cardio-respiratory exercise for a minimum of 3 days per week according to ACSM physical activity guidelines). The main outcome measure is BMD of the hip and lumbar spine measured by dual-energy x-ray absorptiometry (DXA). A History of Leisure Activity Questionnaire was administered to quantify lifetime weight bearing physical activity. Linear regression model was used to test for group differences in spine and hip BMD, controlling for age, body weight, lifetime weight bearing physical activity, menstrual status, and hormone supplementation.

Results: BMD in competitive master age female cyclists (Hip = XX; Spine = XX) was significantly (p<0.001) lower compared to their normally active female counterparts (Hip = XX; Spine = XX). A greater lifetime history of weight-bearing activity was associated with a higher BMD at both the hip and spine. Cyclists were X times more likely (Odds Ratio, 95% CI) to have osteopenia in the spine or hip compared to controls. Longer history of exclusive participation in cycling was associated with lower hip and spine MD.

Conclusions: Master female cyclists with history of exclusive training in the NWB sport of cycling have lower hip and spine BMD than their peers of similar age and may be at risk for developing poor bone health.
Background: Differentiation of mouse stem cells into neuronal cells is a complex and poorly understood process. Previous research has shown retinoic acid (RA) to be an important regulatory factor of differentiation and proliferation of embryonic stem cells, both in-vitro and during postnatal neurogenesis. This process has yet to be explored, however, within the context of adult neuroprogenitor cells. A better understanding of this process may aid in developing methods to enhance neurogenesis in regions of cerebral ischemia following stroke. In this study, we hypothesized that addition of retinoic acid would decrease the overall proliferation of neuroprogenitor cells in a concentration dependent manner through an increase in the rate of cell death.

Methods: Neuroprogenitor cells were harvested from adult mice. Cell cultures were prepared and from our initial cultures, experiments were run to both directly and indirectly assess proliferation. 2 x 10^6 cells per well were plated in neurobasal medium with appropriate growth factors including B27(-insulin), FGF2 and IGF-1. Additionally, retinoic acid was added in concentrations of 2.5 uM, 5 uM, and 10 uM, along with DMSO control. Proliferation was assessed 3 days after plating by direct cell count as well as by MTT assay. Cell death assays were attempted by LDH assay but successful results were not obtained. The cells from each of the constructs were preserved and are currently being used to look for expression of key genes involved in proliferation, however this data is not presented here.

Results: Based on direct counts, the average number of cells per well are as follows. The control wells had an average of 2.82 x 10^6 cells per well. 2.5 uM RA wells had an average of 1.84 x 10^6 cells per well. 5 uM RA wells had an average of 1.46 x 10^6 cells per well. 10 uM RA wells had an average of 1.3 x 10^6 cells per well. Results from the MTT and LDH assays are forthcoming.

Conclusions: Our findings support our original hypothesis that RA appears to down-regulate proliferation of adult neural stem cells. Additionally, these results support the conclusion that this inhibition occurs in a concentration dependent manner. Further studies are needed to elucidate whether this inhibition is due to increased cell death or a decrease in the rate of cell division. Additional studies are also currently underway to explore whether RA affects expression of key genes involved in apoptosis and regulation of cellular proliferation.
Title: INVESTIGATIONS OF THE IMPACT OF MICROCHIMERISM ON T CELL CLONES-SPECIFIC FOR NON-INHERITED MATERNAL ANTIGENS

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Mentor(s): William J. Burlingham, PhD

Support: Shapiro Summer Research Program and Department of Surgery

Background: The placental barrier between the mother and the fetus is not absolute, and it has been shown that the exchange of certain cells across this barrier can occur in both directions. During pregnancy and nursing, maternal substances and immune cells can enter the offspring’s bloodstream and may induce a lifelong tolerance to these antigens. This is the basis for maternal microchimerism. Understanding of the underlying mechanisms for this phenomenon may lead to development of techniques that allow drug-free acceptance of transplanted grafts. In mice and human, developmental exposure to non-inherited maternal antigens (NIMA) produces variable immunologic effects in the offspring, depending on the balance of NIMA-specific T regulatory vs. T effector cells populations. Our hypothesis is that maternal microchimerism (MMc) will induce deviation of maternal antigen-specific T cells into TGF-β-producing T regulatory cells, which block the proliferation of effector T cells, and are important in allograft tolerance.

Methods: Breeding scheme: male B6 (H2b/b) transgenic (TEA +/-) Thy1.1/Thy1.1 mice were crossed with female BDF1 (H2b/d) wild type (TEA -/-) Thy1.2/Thy1.2 mice. 25% of F1 offspring are expected to be TEA+/- and H2b/b (exposed to maternal antigen d, i.e. NIMAd). The control group is termed NIPAd (non-inherited paternal antigen) and was generated by reversing the sexes (female B6 were crossed with male BDF1). Flow Cytometry: Spleen, thymus, LNs, and blood cells were quantified using PE-labeled anti-H2Kd, along with other FITC-, PB-labeled antibodies. B6 and BDF1 cells were used as negative and positive controls, respectively. The data were analyzed using FlowJo software. In-vivo MLR: 2x10^5 CFSE-stained NIMAd TEA cells were injected into BDF1 mouse, and TGF-β expression was measured using flow cytometry.

Results: Clonal deletion effect in NIMA^d^-exposed offspring was demonstrated with flow cytometry. NIMA^d^-exposed mice (b/b) have no E-alpha peptide, and as a result, their TEA cells (vβ6+/vα2+) are not deleted during T-cell development. The variability in the percentage of vβ6+/vα2+ TEA cells in CD4+ population was found to be dependent upon the amount (if any) of MMc. In contrast, (b/d) mice have E-alpha peptide, and very few TEA cells remained. In the in-vivo MLR experiment, the amount of TGF-β expression was expected to be increased. However, the result was inconclusive, probably due to the relatively small number of cells injected.

Conclusions: Since the in-vivo MLR experiment was inconclusive, it is still early to determine the exact effect of MMc on TGF-β producing T regulatory cells. Nevertheless, future directions have been planned in order to gain more insight into this problem. These include injecting more splenocytes into BDF1 mice, performing in-vitro MLR, and determining NIMA effects on both Thy1.1 and Thy1.2 populations.
Background: Renal dysfunction accelerates the pace of cardiac hypertrophy and may lead to impaired diastolic function (DF) and rapid disease progression in outpatients with heart failure (HF). We investigated the utility of assessing changes in glomerular filtration rate (GFR) and echo grading of DF to predict risk of death/hospitalization in a referral cohort of outpatients with chronic HF.

Methods: We studied 135 participants enrolled in a multicenter cohort study of outpatients with chronic heart failure who had echo assessment of DF and serial measures of GFR over 16 ± 9 months of enrollment. GFR was calculated using the Modification of Diet in Renal Disease equation. DF was graded using American Society of Echocardiography guidelines. We used constructed multivariable models to test whether baseline DF grade and change in GFR were independent predictors of death/hospitalization due to worsening HF. Potential confounders included age, sex, HF etiology, ejection fraction (EF) and change in EF over time, BMI, and diabetes.

Results: The mean ± SD age of participants was 57±14 years; 69% were male. Of the 135 patients, 30% had HF with normal EF. Of the remaining patients, 55% were non-ischemic, 37% were ischemic, and 8% other. Over a mean follow-up period of 16 months, 37 participants experienced an endpoint event. Baseline diastolic dysfunction grade (p=0.019) and change in GFR (p=0.033) over time independently predicted risk of adverse outcome. Relative risk (RR) increased as diastolic dysfunction grade worsened (Grade 1 = 1.2, Grade 2 = 1.6, Grade 3 = 2.0). Any decrease in GFR during f/u was associated with a RR of 1.7. For patients with baseline creatinine > 1.5 mg/dL and a decrease in GFR during f/u, the RR was 2.6. After accounting for DF and GFR over time, change in EF (p=0.754) and presence of diabetes (p=0.934) did not independently predict outcome.

Conclusions: Our findings suggest that DF grade and change in GFR over time may improve prediction of adverse events in HF patients irrespective of the degree of systolic dysfunction. These parameters should be studied in larger cohorts with longitudinal data as a means to improve our ability to assess prognosis in heart failure.
THE EFFECT OF SHEAR STRESS ON ENDOTHELIAL NITRIC OXIDE SYNTHASE ACTIVITY IN OVINE ENDOTHELIAL CELLS: A PRELIMINARY MODEL

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Support: Shapiro Summer Research Program and the UW Cardiovascular Research Center

Background: Maintenance of physiologic laminar blood flow (i.e. shear stress) is crucial for normal vascular functioning. In fact, alterations in shear stress have been directly implicated in the pathogenesis of several cardiovascular diseases including hypertension, atherosclerosis and preeclampsia. In normal vasculature, shear stress is a powerful activator of endothelial nitric oxide synthase (eNOS) activity (via multi-site phosphorylation) and leads to increased nitric oxide (NO) production. NO acts as a potent vasodilator and thus normalizes the shear stress on blood vessel walls. In addition to changes in phosphorylation state, it has been suggested that the location of eNOS within endothelial cells significantly regulates NO biosynthesis. We hypothesize that acute increases in shear stress result in the association of eNOS with a diverse family of protein partners that regulate its sub-cellular localization, catalytic function, and biological activity. In order to investigate the molecular mechanisms underlying sub-cellular eNOS movement and the precise partitioning of the eNOS protein under physiologic flow, we have developed a model using ovine uterine artery endothelial cells.

Methods: Ovine uterine artery endothelial cells harvested from live animals during the follicular phase of the ovarian cycle were grown on glass slides under static conditions until 80-100% confluent. Subsequently, the cells were either placed in a chamber with laminar flow for 10 minutes, which exposed them to physiologic levels (15 dynes/cm²) of shear stress (experimental group), or left in static conditions (control group). The cells were lysed, their protein content was separated from other cellular components, and a western blot was performed to compare the qualitative amounts of Ser635-phosphorylated eNOS (a surrogate marker for eNOS activity) between the control and experimental groups.

Results: A two-fold increase in Ser635-phosphorylated eNOS was observed in endothelial cells exposed to shear stress compared with static controls. This finding was confirmed in cells from two different animals.

Conclusions: This preliminary experiment confirms that exposure to 15 dynes/cm² of shear stress for 10 minutes induces significant eNOS activation in ovine uterine artery endothelial cells. Future studies will use the protocol established with this study followed by confocal microscopy, immunoisolation, and fractional isolation to investigate how eNOS (in its various phosphorylation states) is temporally and spatially re-partitioned in response to acute shear stress.
Title: PREVALENCE, INCIDENCE AND TEMPORAL TRENDS OF KIDNEY STONES IN A RURAL WISCONSIN POPULATION

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Support: Shapiro Summer Research Program and Department of Urology

Background: Previous epidemiological research estimates the current risk for stone disease at 12% for men and 6% for women in the United States and suggests that the incidence of stone disease is increasing. The cost of stone disease in the United States was estimated at $2.1 billion in 2000. Epidemiological approaches in stone disease research will enhance our understanding of the natural history of urolithiasis and facilitate the development of appropriate preventive measures to reduce the incidence and economic burden on those affected. Knowledge of the characteristics of Wisconsin residents with stone disease will help identify demographic trends and, potentially, risk factors specific to this population. We anticipate that this research will be used to shape treatment guidelines and standards of care for the management of kidney stone disease.

Methods: A computerized query was developed to identify kidney stone diagnoses made at the Marshfield Clinic from 1979-2008 using ICD-9 codes 592.0, 592.1, and V13.01 for patients living within the 24-zip code Marshfield Epidemiological Statistical Area (MESA), one of the nation’s largest electronic databases of patients’ medical records. Patient data collected included demographics, comorbidities, and treatment procedures. Incident cases were identified as the first recorded diagnosis of kidney stones. Additional diagnoses occurring >3 months after the incident diagnosis were classified as recurrent episodes. Incidence and prevalence were calculated using population data and rate macros maintained by the Marshfield Clinic Research Foundation. Manual abstraction was conducted on 230 patient records to assure validity of the query.

Results: A preliminary query identified 39,652 diagnoses of kidney stones among 5,695 unique individuals. Data collection and analyses are underway for the finalized query and will include total number of cases per year, age-adjusted incidence and recurrence rates by year since 1992, incidence and recurrence rates stratified by age and gender since 1992, point prevalence at the end of every year from 1992-2008, prevalence of individuals with history of only one lifetime stone event, prevalence of individuals with ≥1 recurrent stone, and changes in rates for each measure over the time period of the study.

Conclusions: We hypothesize that the prevalence and incidence of kidney stones in a Wisconsin population, specifically the Marshfield Epidemiological Study Area (MESA) population, is higher than national rates. Furthermore, we hypothesize that the incidence of kidney stones is increasing in women and not changing in men.
Title: CAREER TRACK EXPERIENCES OF WOMEN PHYSICIANS: A QUALITATIVE STUDY OF LIFE CHOICES IN MEDICINE

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Mentor(s): Carol Isaac, PhD, PT

Support: Shapiro Summer Research Program and Department of Medicine

Background: According to the Association of American Medical Colleges (AAMC, 2008), in 2007-08, women accounted for 34% of all medical faculty and 17% of full professors. Although women have comprised over 30% of medical students for nearly three decades, there has been a disproportionate lack of advancement of women physicians into senior and leadership positions. (Carnes, 2008; Phyllis L. Carr & al., 1998; P. L. Carr, Szalacha, Barnett, Caswell, & Inui, 2003; Tesch, Wood, Helwig, & Nattinger, 1995) Significant bodies of research, including studies by the AAMC and the Association for Women in Science have identified difficulties in work-family and/or work-life balance as a significant cause of the “disproportionately high departure rate” for women from the academic medical arena (AAMC, 2008; Buddeberg-Fischer, Stamm, Buddeberg, & Klaghofer, 2008; Howell, Joad, Callahan, Servis, & Bonham, 2009; Jovic, Wallace, & Lemaire, 2006; Leboy, 2009; Shollen, Bland, Finstad, & Taylor, 2009). The National Academy of Sciences concluded that inequities arising from systematic gender bias pose the greatest barrier to achieving gender equity; however, other research points toward the collision between the ticking biological and tenure clocks (Fox, Schwartz, & Hart, 2006). Many recent studies document the difficulties of work-family balance for women in medicine (Buddeberg-Fischer et al., 2008; Howell et al., 2009; Jovic et al., 2006; Shollen et al., 2009); however, very few qualitative studies examine this specifically. (Mobilos, Chan, & Brown, 2008; Yedidia & Bickel, 2001). In addition, the impact these career tracks have had on family, and professional lives has yet to be fully investigated. To explore these issues in residents and faculty in internal medicine at the University of Wisconsin-Madison (UW), we interviewed residents and faculty in the Department of Medicine at the UW.

Methods: A qualitative study composed of semi-structured, in-depth interviews was conducted with 34 faculty and 18 residents of the Department of Medicine. Men and women were randomly selected to represent the following career tracks: Clinic Health Sciences (Clinician-Educator), Tenure (Clinician-Researcher), Clinical (Clinician-Practitioner), PG3s and PG1s. Questions covered topics of balance, career choices and support networks. A grounded theory approach facilitated the analysis of common themes between groups, within groups and as a cohort.

Results: Preliminary analysis indicates that even though 63% of women’s compared to 37% of men’s text discussed balance strategies, women physicians’ text illustrated decreased support (70%/30%), uphill struggles (62%/38%), personal and career consequences (69%/31%) and a perceived lack of respect (92%/8%). Although men were more concerned with control of time (41%/59%), women more frequently discussed importance of mentors (60%/40%) and juggling roles (67%/33%).

Conclusions: This exploratory study illuminates the career process and the effect on their personal lives. A second phase will involve interviewing their spouses/partners.
Title: VIEWS OF ADOLESCENTS ON TECHNOLOGIES TO PROMOTE AND IMPROVE FITNESS

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Background: Obesity is a significant health problem affecting adolescents. Obtaining in-person education and motivation to improve physical activity and lifestyle choices is problematic for most adolescents. The widespread use of technology by adolescents may provide new opportunities to promote physical activity. The purpose of this study was to investigate current use of communication technology by adolescents, preferences by gender, and perspectives on how technology could be used in the future to increase physical activity and improve fitness.

Methods: Participants between the ages of 11-18 years old were recruited from a general pediatric clinic and completed a 10 question paper survey. Questions examined concerns about weight, and assessed use of six technologies: social networking sites, email, cell phone, text messaging, Ipod, and video games.

Results: Surveys were completed by 101 participants (84% response rate). They were 67% female and had a mean age of 15.5 years old. Most participants (52%) were being seen at the clinic for health supervision. Of those who responded, 90% had concerns about their weight, regardless of gender. For all six technologies assessed, reported use was greater than 70%, regardless of gender. Three technology choices were equally favored for future use as a fitness-improving method (1) emailing a health care provider or nurse, (2) utilizing a GPS device, and (3) Ipod + Nike (accelerometer).

Conclusions: The majority of adolescents in a clinic setting report concern about their weight, and are already utilizing many different forms of technology for communication. This familiarity with communication technology offers new opportunities to promote and reinforce physical activity and improved fitness in adolescents. Future studies are needed to explore potential differences in technology preferences between males and females and the effectiveness of technology-based interventions to promote fitness in adolescents.
Background: The balance of phosphatidylethanolamine (PE) and phosphatidylcholine (PC) is regulated in large part by the methionine cycle. Research done on human samples by the Patti Lab has shown that the ratio between PE and PC changes in insulin resistant patients versus DM2 patients. Lastly, the Patti Lab has found that the naturally occurring compound betaine, a methyl donor that plays a crucial role in the methionine cycle, is significantly higher in insulin sensitive (IS) individuals versus insulin resistant (IR) individuals. The pathway using betaine (the PEMT pathway) accounts for 1/3 of the PC in humans. The other 2/3 comes from the choline pathway. PC from the choline pathway has different side chains (principally arachidonic acid, associated with inflammation) than PC from the PEMT pathway (principally vaccinic acid, associated with IS). The lipidomics data from the Patti Lab samples confirm this trend.

Methods: Given the data presented above we hypothesized that perturbations in the methionine cycle may lead to insulin resistance and that betaine supplementation may mitigate these changes by restore the perturbations in PC biosynthesis. To test this hypothesis we used a mouse model using C57BL/6J mice aged 6 weeks. Mice were fed either a 60% fat diet proven to induce insulin resistance or a chow diet. We further divided these two groups into 0% betaine, 1% betaine and 3% betaine (dissolved in water) diets such that there were six groups. We measured the weight of the mice and the amount of food and water they consumed regularly. At day 24 we did a fasting glucose tolerance test (GTT)

Results: We found that mice on the betaine diet had better glucose tolerance and that mice on both the high fat and chow diets gained less weight than mice on given water as a control.

Conclusions: This indicates that betaine supplementation by aid in preventing the onset of DM2. Tissue studies and large murine studies need to be done to confirm and develop these results.
Title: FIGHTING CANCER THROUGH IMPROVED GOVERNANCE: LESSONS FROM THE U.S. AND THE EUROPEAN UNION

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Mentor: Thomas R. Oliver, PhD, MHA

Support: Shapiro Summer Research Program and Department of Population Health Sciences

Background: The Obama administration’s commitment to a renewed campaign against cancer provides a timely platform to examine how new forms of regulation and governance can be utilized to improve cancer detection, treatment and survivorship. “New governance” is a regulatory model that differs from top-down, command and control regulation and from professional self-regulation. Instead, it relies on effective collaboration from multiple stakeholders, and emphasizes improved efficiency and innovation through data collection, monitoring and benchmarking. The objective of the paper is to explore how the contemporary campaign against cancer can improve health outcomes by incorporating new resources and improved governance to bridge the gap between research and clinical care.

Methods: A literature review was conducted in political science, oncology, law, and health policy in the U.S. and Europe. Interviews were conducted with cancer survivors, advocates, oncologists, researchers, health policy experts, and quality improvement administrators.

Results: Despite spending over $200 billion on cancer research over the past twenty years, reductions in cancer mortality have been relatively weak compared to more rapid progress in heart disease and other major health threats. Additionally, there has been uneven progress in treating different types of cancers. Between 1975 and 2001, 5-year survival for Acute Lymphoblastic Leukemia improved from nearly 15% to 60% while lung cancer survival increased modestly from 11.9% to 15.6%. These disparities follow a similar trend in clinical trial participation, as ALL and other childhood cancers achieve nearly 70% participation in clinical trials while less than 3% of adults enroll in clinical trials. Networks like the Children’s Oncology Group (COG) attribute much of their success to their unique organization and utilization of new tools and information. Examples of these new practices include the growing use of protocols and clinical guidelines and the increasing focus on information gathering and public reporting.

Conclusions: We have argued that the U.S. system of cancer care is poised to take advantage of new information, participants, and funding streams that have emerged in recent years. The progress in childhood leukemia and the Europe Against Cancer program demonstrate that the chief barrier to reducing the threat to public health posed by cancer is not a lack of financial resources, but rather a lack of new institutional arrangements and tools that could accelerate learning and practice across cancers, patient populations, and geographic locations. Modest steps toward a new performance regime—broader use of HIT and registries, development of clinical protocols, new system-wide goals, and public comparison of outcomes—can be taken by leaders within the cancer network. We believe these steps would trigger a dynamic process of innovation and system improvement. However, substantial barriers exist. Future research will focus on the impact of these barriers: ineffective regulatory institutions, conflicts of interest and ensuing lack of trust in clinical trials, and inadequate incentives for monitoring and reporting health outcomes.
Title: IS RAPID VASODILATION IN RESPONSE TO SINGLE CONTRACTIONS IMPAIRED IN HUMAN OBESITY?

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Background: Mechanical factors associated with muscle contraction may influence vascular responses to exercise.

Methods: We tested the hypothesis that rapid vasodilation in response to single dynamic forearm contractions would be reduced in young obese adults (n=14, BMI 37±1) when compared to lean controls (n=15, BMI 21±1). We measured heart rate (ECG), blood pressure (BP, arm cuff & Finapress), and forearm blood flow (FBF, Doppler ultrasound) during a single forearm contraction (performed in triplicate) at 15, 30, and 50% of forearm maximal voluntary contraction (MVC). To account for higher BP in obese subjects, we assessed forearm vascular conductance (FVC=FBF/BP). Regardless of differences in baseline FVC, a given % change in FVC from baseline (%ΔFVC) will reflect the same % change in vessel radius (ie vasodilation). Therefore, we compared %ΔFVC between groups at each intensity.

Results: At rest, FVC was higher in obese (p<0.05). With contraction, the %ΔFVC was intensity-dependent (50%>30%>15%) and peaked within 4-6 cardiac cycles after contraction in both groups. The %ΔFVC was similar at 15% between groups, but significantly lower in obese subjects at 30 and 50% MVC (p<0.05).

Conclusions: These results indicate that with increasing intensity, obese adults exhibit reduced rapid vasodilation in response to a single dynamic forearm contraction.
Title: VALIDATING AGING-RELATED BRAIN MAPPING CHANGES IN WORKING MEMORY UTILIZING ACUTE STROKE PATIENTS

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Background: The Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model is based on neuroimaging findings in several cognitive tasks that show older adults have more bilateral hemispheric activation than younger adults who show more lateralized activation (Cabeza 2002).

Activity in the left hemisphere has been associated with verbal working memory (WM), while activity in the right hemisphere has been associated with both verbal and spatial WM (Rypma et al 1999, Prabhakaran et al 2000). Philipose et al (2007) have shown that unilateral stroke differentially diminishes performance in these tasks depending on the hemisphere affected. Specifically, right cortical stroke patients are impaired in both spatial and verbal WM tasks, while left cortical stroke patients have impaired verbal WM.

Methods: Here, we use data from acute unilateral stroke patients to directly test the HAROLD Model. Stroke was defined as acute infarct on diffusion weighted imaging and/or hypoperfusion on perfusion weighted imaging with corresponding neurological deficits. Patients were studied within three days of symptom-onset. Younger adults (age ≤50) and older adults (age >50) with unilateral acute stroke, as well as different control populations performed both a verbal and spatial item-recognition delayed WM task. A subject paced-design (variable encoding, retrieval time) with a fixed maintenance interval of 5000 msec and varying working memory loads of 3-6 items for verbal and 1-4 items for spatial WM tasks was used. Subject performance in terms of encoding time, retrieval time, and accuracy was compared to control groups. Control groups included young and old healthy adults, as well as young and old transient ischemic attack (TIA - defined as resolution of symptoms in 24 hours and exclusion of stroke on MRI) patients. TIA patients were enrolled in order to control for brain vasculopathy changes as well as hospitalization-associated stressors and medications. All subjects were right handed. We hypothesized that unilateral stroke to either hemisphere would disrupt both spatial and verbal WM in older adults due to the bihemispheric activations associated with performance of these WM tasks.

Results: We found that performance for both spatial and verbal WM was worse in older patients with unilateral stroke to either the left or right hemisphere in comparison to the different controls.

Conclusions: These data support the HAROLD model and is also consistent with the hypothesis that increased bilateral activation reflects compensatory recruitment in order to counteract normal aging effects on cognition (Cabeza et al 1997, 2002).
Title: GLUTAMATE IMMUNOCYTOCHEMICAL STAINING IN A Rhesus Macaque With Experimental Glaucoma

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Mentor(s): T. Michael Nork, MD, MS

Support: Shapiro Summer Research Program and Department of Ophthalmology and Visual Sciences

Background: Glaucoma is one of the leading causes of blindness in the world. Chronically elevated intraocular pressure (IOP) is thought to directly harm the optic nerve leading to loss of vision. Although this neurotrophic hypothesis is almost universally accepted by experts, recent experimental results were not predicted by this hypothesis. Nork and al. showed that ganglion cells overlying retinal laser spots were able to survive in chronically elevated IOP in a monkey model of glaucoma. The excitotoxic hypothesis was proposed to explain this phenomenon. High IOP first impairs the function of photoreceptor cells via a reduction in choroidal blood flow. Impaired photoreceptor cells then fail to re-uptake excitatory neurotransmitter glutamate from the synaptic cleft, which triggers off-bipolar cells to release an excessive amount of glutamate. The accumulation of extracellular glutamate ultimately leads to programmed cell death of ganglion cells and loss of sight.

Methods: Immunocytochemical analysis was used to detect glutamate in the retina of a rhesus monkey, which underwent unilateral laser trabecular meshwork destruction in one eye to induce elevated intraocular pressure. The normal fellow eye was used as a control.

Results: The experimentally glaucomatous eye showed a marked increase in immunostaining for glutamate in the outer plexiform layer in comparison to the normal fellow eye.

Conclusions: The results are consistent with the hypothesis that glutamate from the photoreceptors plays a role in the demise of ganglion cells in glaucoma. However, larger cohort of monkeys is needed to validate the findings.
CHARACTERIZATION OF TWO C-TYPE LYSOZYMES IN THE MALARIA VECTOR ANOPHELES GAMBIAE

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Malaria is a devastating disease, killing about 2 million people each year. It is caused by a protozoan parasite of the genus Plasmodium that depends on Anopheles mosquitoes for transmission. Understanding of the mosquito-parasite relationship will allow for more sophisticated transmission-blocking. Previous research has shown decreased parasite survival after the knockdown of a c-type lysozyme in the mosquito (Lys c1), suggesting that the parasite benefits from the presence of this protein. Lysozyme is a protein that is found in many organisms; however Anopheles gambiae is unusual in that it has eight c-type lysozyme genes, which are all expressed at some point in its life cycle. The purpose of this experiment was to begin to characterize two of these additional lysozyme genes (Lys c7 and Lys c8) via protein expression and gene knockdown in adult mosquitoes.

Methods: For the protein expression portion of this experiment the Drosophila S2 insect cell expression system was used. Each gene was amplified from an existing Anopheles cDNA isolate, cloned into the pMT vector for amplification in E. coli. These plasmids were then transfected into competent S2 cells (Invitrogen) for both stable and transient expression. The protein was purified using nickel agarose and analyzed by Western blot. For the gene knockdown portion of the experiment, double stranded RNA (dsRNA) was created using gene specific primers and the MEGAScript RNAi kit (Ambion) according to manufacturer's instructions. Approximately 0.3 ul of this dsRNA was injected into adult mosquitoes to induce knockdown at 1 and 4 days post injection.

Results: Both Lys c7 and Lys c8 were successfully cloned into the pMT vector and confirmed by sequencing. Successful transfection was confirmed by a GPF-containing control, however; transient expression studies were inconclusive in this insect cell expression system. For both genes, gene specific dsRNA was produced, and knockdown was confirmed compared to a GFP injected control group of mosquitoes.

Conclusions: Proteins were not detected using the Drosophila S2 cells, so future research will attempt expression of these proteins in E. coli using the Flexi-vector expression system (Promega), to attempt to isolate an adequate quantity of correctly folded protein for in-vitro activity assays. Since gene knockdown has been confirmed, future work will include challenging these knockdown mosquitoes with Plasmodium infection to help to determine the relationship between these proteins and the malaria parasite.
Title: SORCIN MODULATION OF Na⁺/Ca²⁺ EXCHANGER ACTIVITY IN ISOLATED CARDIOMYOCYTES

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Mentor(s): Hector Valdivia, MD, PhD

Support: Shapiro Summer Research Program and UW Cardiovascular Research Center

Background: Regulation of Ca²⁺ ion currents is a crucial homeostatic priority in a normally functioning cardiomyocyte, and dysregulation of Ca²⁺ fluxes via altered activity of excitation contraction coupling (ECC) proteins has been implicated in the pathogenesis of diseases such as heart failure and some genetic dysrhythmias [1]. This study aims to investigate the interaction of two ECC proteins: Sorcin and the sarcolemmal Na⁺/Ca²⁺ exchanger (NCX).

Methods: NCX activity in isolated cardiomyocytes from Sorcin knock-out (KO) mouse models was compared to NCX activity in wild-type cardiomyocytes as measured by caffeine induced Ca²⁺ transient decay using confocal microscopy.

Results: The mean rate of decay in the Sorcin KO model was significantly faster than in the control group when the cell were not perfused with Isoproterenol (τ = 1091 +/- 71 mSec vs τ = 1336 +/- 74 mSec, p = 0.024). However, when the cells were perfused with Isoproterenol, there was no significant difference between the groups (τₘₒ = 1995 +/- 117 mSec vs τₚₚ = 1724 +/- 125 mSec, p = 0.12).

Conclusions: The loss of Sorcin appears to increase the activity of the NCX at rest but this modulation appears to be lost in the presence of beta adrenergic stimulation. Further investigation to elucidate the mechanism of Isoproterenol modulation could include using inhibitors such as H89 (PKA inhibitor), KN-93 (CaMKII inhibitor) or forloskin (cAMP activator) in similar experiments.
Title: THE ROLE OF THE ARYL HYDROCARBON RECEPTOR IN TRANSPLANTATION: THE EFFECTS OF THE AHR ACTIVATION OR DELETION ON SKIN GRAFT SURVIVAL

Authors: S. Kyle Pauly BS; John Fechner MS; Xiaoji Zhang MS; Chris Bradfield, PhD; Josh Mezrich, MD.

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Mentor(s): Josh Mezrich, MD, John Fechner, MS

Support: Department of Surgery NIH/NIDDK T35 Grant

Background: The Aryl Hydrocarbon Receptor (AHR) is a cytosolic transcription factor with numerous endogenous and xenobiotic ligands, most notably 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Activation of the AHR has been shown to alter thymus function, dendritic cell activation, and recently T cell differentiation. The most intriguing and controversial of this data, is that TCDD may induce regulatory T cells, while a second AHR ligand, FICZ, promotes Th17 differentiation. This lead us to test whether injection of recipient mice with either TCDD or FICZ altered skin allograft rejection in a fully mismatched mouse model.

Methods: TCDD was given to recipient C57BL/6 mice intraperitoneally (IP). 24 hours later, donor skin was grafted from BALB/c mice, and deemed rejected when 80% was lost. For experimentation of FICZ, dosing was performed IP on day -1 and 3 relative to skin grafting. Skin grafts, thymus, and spleen were harvested for histological examination and in vitro experiments.

Results: Skin graft survival was significantly prolonged in the dioxin treated group. In vivo exposure with TCDD lead to significant FoxP3+ Treg generation in all tissues analyzed. Skin graft survival across a full MHC mismatch (BALB/C to C57BL/6) was significantly prolonged in the TCDD treated group (GST = 22, 35, >10, >10, >16, >16) compared to untreated controls (GST = 10, 10, 13, 13, 19). This finding was confirmed with cohorts of mice sacrificed at day 10 and 16, revealing histologically viable grafts in the treated group and complete necrosis in controls. Flow cytometric analysis of thymocytes harvested at day 10 showed altered differentiation patterns in treated mice. Analysis of day 10 splenocytes revealed that treatment resulted in a lower frequency of activated/memory CD8 T cells. Specifically, treated recipients had fewer recently-proliferated (Ki67) CD8 T cells and fewer effector/memory phenotype (CD44 hi, CD62L lo, b7integrin lo) CD8 T cells than controls. Ongoing studies of FICZ treated recipient mice show similar or perhaps quickened rejection times compared to control mice, but no prolonged graft survival rates. Unlike CD8 T cells from TCDD treated mice, flow cytometry performed on cells taken from the spleens of the FICZ treated recipient mice do not show differences in T cell differentiation between FICZ and control groups.

Conclusions: A single pretransplant TCDD dose impairs skin graft rejection by altering the CD8 T cell response to alloantigen, and possibly inducing graft-protective FoxP3+ Tregs. FICZ upregulates TH17 effector cells in vitro, and experiments investigating its role in vivo are ongoing. This confirms that the recent excitement identifying this receptor as a central regulator of T cell differentiation and rapid thymic involution correlates with graft prolongation in a relevant transplant model. This work will identify an entirely new target for strategies of tolerance in organ transplantation.
Title: MYBPC-NULL MOUSE HEART HAS INCREASED BASAL ENERGY REQUIREMENT

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Mentor(s): J. Carter Ralphe, MD; Willem J. DeLange, PhD

Support: Shapiro Summer Research Program and UW Cardiovascular Research Center

Background: Hypertrophic cardiomyopathy (HCM) is an autosomal dominant genetic disease characterized by asymmetrical ventricular hypertrophy, interstitial fibrosis and myocardial disarray. Mutations in beta myosin heavy chain and cardiac myosin binding protein C (cMyBP-C) account for over 65% of all mutations that cause HCM. There are, however, at least six other HCM-causing mutations involving sarcomeric proteins. Therefore HCM is considered a disease of the sarcomere. The classical view of HCM pathogenesis is that compensation for decreased contractility leads to hypertrophy and remodeling. This, however, seems incongruent with clinical and molecular findings. Instead, we hypothesized that increased energy demand leading to energy depletion may underlie HCM. Previous observations that increased number of mitochondria and upregulation of certain metabolic genes are caused by cMyBP-C mutations supports this hypothesis. Although the role of cMyBP-C in cardiac pathophysiology is not fully understood, it is well established that cMyBP-C can modulate contraction following PKA-mediated phosphorylation of specific sites. Unphosphorylated cMyBP-C binds the S2 subfragment of the myosin head acting as a tether that hinders crossbridge cycling and reduces actomyosin ATPase. If cMyBP-C is phosphorylated or ablated, myosin heads take on a position more favorable for crossbridge formation resulting in increased calcium sensitivity and force production. In order to test the hypothesis that energy depletion underlies HCM, and using a cMyBP-C knockout mouse model (cMyBPC-KO), we designed and implemented an ATPase assay to measure the crossbridge cycling activity in cMyBPC-KO and WT mouse hearts. We speculated that the cMyBPC-KO hearts will have increased actomyosin ATPase activity when compared to WT hearts due to the release of the tether on crossbridge cycling.

Methods: cMyBPC-KO and WT mice were sacrificed at ten days after birth and their hearts extracted following proper protocol. These hearts were then used to make Myofibrils which were in turn employed as substrate in ATPase assays. ATP consumption by the actomyosin ATPase was coupled with metabolic enzymes that generated pyruvate, NADH and ultimately NAD+. By recording NADH fluorescence decay, we were able to monitor ATP turnover in the reaction. A buffer solution containing the appropriate calcium concentration (pCa) was implemented.

Results: Although there was a trend towards marginal increase in ATPase turnover rate in cMyBPC-KO hearts at ten days after birth, this increase did not reach statistical significance.

Conclusions: The lack of a significant difference between the rate of ATP turnover in cMyBPC-KO and WT hearts indicates that the kinetics of contractility may not be affected by the ablation of cMyBP-C. Alternatively, it is possible that alterations in ATP turnover rates may only become apparent in adulthood or after environmental insult. Our general hypothesis that energy depletion underlies HCM therefore requires further testing and research.
Title: INFLAMMATORY EFFECTS OF LARYNGITIS-ASSOCIATED PATHOGENS (HELICOBACTER PYLORI, STAPHYLOCOCCUS AUREUS AND STAPHYLOCOCCUS EPIDERMIDIS) ON VOCAL FOLD FIBROBLASTS

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Mentor: Susan Thibeault, PhD

Support: T35 NIH short term training grant: DK 062709-0401 and by RO1 DC 9600 from the National Institute on Deafness and other Communication Disorders.

Background: Chronic inflammatory conditions of the larynx affect up to 20% of Western populations. Other investigators have reported the presence of H. pylori, S. aureus and S. epidermidis in patients with laryngeal lesions and/or chronic laryngitis. However, there is little information on how specific bacteria colonizing the larynx can alter the immunological microenvironment and their pathogenic role in the development of chronic inflammatory states. We hypothesize that changes in immunologically-relevant cellular markers (specifically, antigen-presenting molecules and inflammatory mediators) observed in response to bacterial challenges in the vocal fold lamia propria can be triggered by changes in the pathogenicity of bacterial flora.

Methods: Using immortalized human vocal fold fibroblasts (hVFF) as our in vitro model we assessed the pathogenicity and contribution of H. pylori, S. aureus, and S. epidermidis to the immunological architecture of the larynx. Cytotoxicity studies were completed for all 3 strains to determine optimal bacterial dilutions that preserve the viability of hVFF after 48 hours incubation. These non-cytolytic dilutions of bacteria were added to confluent monolayers of human vocal fold fibroblasts (hVFFs). After 48 hours incubation, the cells were fixed for immunoflorescence and the supernatants were collected for ELISA. For immunomodulation markers we looked at the expression of MHC Class II and CD1d. The supernatants were used to quantify the presence of a chemoattractant (monocyte chemoattractant protein MCP-1) of immune cell helpers, the inflammatory (IL-6) and remodeling cytokines (IL-1β).

Results: The non-cytolytic dilution was 0.12 colony-forming units (CFU) per 100,000 hVFF for S. aureus and 130 CFU/100,00 hVFF for S. epidermidis, indicating that S. aureus is more cytolytic to hVFF than S. epidermidis. After infection with S. epidermidis IL-6 (437.6 pg/mL) and MCP-1 (211.6 pg/ML) were lower than the IL-6 (718.3 pg/mL) and MCP-1 (302.5 pg/mL) release after infection with S. aureus. IL-1β was below detection for all 3 strains. The hVFF infected with S. epidermidis expressed CD1d, and little MHCII, while those infected with S. aureus expressed both immune markers.

Conclusions: Understanding how the bacteria flora affects mucosal immunity, what the tolerance limits for the local cells and immune response are, as well as how it is affected by chronic inflammatory insults, may allow us to manipulate the flora microenvironment (i.e. by altering pH or bacterial adhesion) with direct, anti-inflammatory, therapeutic benefit. Determining the pathogenecity of H. pylori to the normal and disease larynx will have far reaching implications in the field of mucosal immunology of the larynx.
PLASMACYTOID DENDRITIC CELL INTERFERON-α RESPONSES IN CHILDREN WITH ASTHMA AND ALLERGIC SENSITIZATION

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Mentors: Robert Lemanske, MD; Daniel Jackson, MD

Support: Shapiro Summer Research Program and Department of Pediatrics

Wheezing rhinovirus (RV) illnesses and allergic sensitization during early childhood are risk factors for childhood asthma development, but the mechanisms underlying these relationships are unclear. Impaired interferon responses are associated with both allergic sensitization and asthma. Plasmacytoid dendritic cells (pDCs) produce large amounts of interferon-α (IFN-α) upon infection with virus. The goal of this study was to determine if children with asthma, particularly those with allergic sensitization, have impaired pDC IFN-α responses.

Blood samples were collected by venipuncture during study visits from children in the Childhood Origins of ASThma (COAST) project at age 10 years. Peripheral blood mononuclear cells (PBMCs) were separated using Ficoll-hypaque density centrifugation, and pDCs were further separated from PBMCs using the EasySep® Human Plasmacytoid DC Enrichment Kit (Stemcell Technologies). Once purified, pDCs were cultured with IL-3 to maintain viability and stimulated with RV and CpG (TLR9 agonist) for 24 hours. IFN-α levels in culture supernatants were analyzed by ELISA. Allergic sensitization was determined by skin prick testing and asthma was diagnosed clinically.

Asthmatic children (n=9) tended to have lower RV and CpG-induced IFN-α responses than non-asthmatic children (n=10) (RV: 437 vs. 589 pg/ml; CpG: 309 vs. 652 pg/ml). Similarly, children with allergic sensitization (n=14) tended to have lower IFN-α responses than children without allergic sensitization (n=5) (RV: 455 vs. 690 pg/ml; CpG: 366 vs. 837 pg/ml). Children with both allergic sensitization and asthma (n=8), in comparison to children without either allergies or asthma (n=4), produced lower levels of IFN-α (RV: 428 vs. 734 pg/ml; CpG: 334 vs. 1019 pg/ml). When samples were processed the same day as the blood draw versus the next day, IFN-α levels on average tended to be higher (RV: 636 vs. 385 pg/ml; CpG: 608 vs. 358). Due to the potential impact of same day vs. next day processing; the data was re-evaluated using only the samples processed on the same day. Children with asthma (n=6) tended to have lower RV and CpG-induced IFN-α levels in contrast to children without asthma (n=10), (RV: 432 vs. 941 pg/ml; CpG: 337 vs.1014 pg/ml). Children with allergic sensitization (n=8) in comparison to children without allergic sensitization (n=2), also tended to have lower RV and CpG-induced IFN-α levels (RV: 577 vs. 869 pg/ml; CpG: 504 vs.1025 pg/ml). Finally, children with asthma and allergic sensitization (n=5) had lower levels of RV and CpG-induced IFN-α levels in comparison to the child without either asthma or allergic sensitization (n=1), (RV: 416 vs. 1224 pg/ml; CpG: 382 vs. 1939 pg/ml).

This preliminary data suggests that children with asthma and/or allergic sensitization tend to have lower levels of RV and CpG-induced pDC IFN-α levels, which may predispose them to virus-induced wheezing and asthma. Additionally, delayed sample processing time may impact IFN-α responses.
Title: CEREBRAL OXIMETRY AS A POSTOPERATIVE MARKER FOLLOWING CARDIOPULMONARY BYPASS

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Mentor(s): Niloo M. Edwards, MD, FACS

Support: Shapiro Summer Research Program and Department of Surgery

Background: Neurologic sequelae remain an intractable source of morbidity in cardiac surgery populations undergoing cardiopulmonary bypass. Other continuous diagnostic technology, such as right-heart catheterization, are not without risk. Continuous cerebral oximetry is a new technology that is non-invasive and provides real-time oxygen saturation of the cerebral circulation. We assess its usefulness as a diagnostic tool in cardiac surgery patients postoperatively.

Methods: Retrospective analysis of 46 patients undergoing cardiac surgery requiring cardiopulmonary bypass. Certain physiologic criteria were defined as critical and then correlated to the patient’s change in cerebral oximetry. Changes in cerebral oximetry where graphed along with changes in hematocrit, mean arterial blood pressure, mean arterial pulmonary pressure, cardiac index, and pH for comparison. Separately, declines of greater than ten and 15 percent from baseline oximetry were defined as critical and then correlated to patients’ length of stay.

Results: A greater than 10% from baseline decline in cerebral oximetry occurred concomitantly with 3 out of 14 (21.4%) instances of a cardiac index below 2, 3 out of 14 (21.4%) instances of a pH below 7.35, and 15 out of 25 (60%) instances of a hematocrit below 28. Patients who experienced less than ten percent decline from baseline cerebral oximetry had an average length of stay of 6.6 +/- 4.0 days. Patients who experienced a greater than ten percent decline had an average length of stay of 12.0 +/- 19.6 days. Patients who experienced between a ten and fifteen percent decline had an average length of stay of 7.9 +/- 4.8 days. Patients who experienced a greater than 15 percent decline had an average length of stay of 15.5 +/- 25.2 days.

Conclusions: Whereas cerebral oximetry does not replace existing technologies and markers in the postoperative management of cardiopulmonary bypass patients, it does independently of those markers predict length of stay.
Title: Surgical Outcomes in the Treatment of Pediatric Patients with Slipped Capital Femoral Epiphysis

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Mentor(s): Kenneth Noonan, MD

Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

Background: Slipped Capital Femoral Epiphysis (SCFE) is one of the most common hip disorders affecting adolescents. It is characterized by the displacement of the femoral neck from the capital femoral epiphysis through the physeal plate. Many conditions are implicit with SCFEs, including endocrine and systemic disorders and especially obesity. Untreated SCFEs is strongly associated with later degenerative hip disorders during middle life and later. SCFEs are further subdivided into stable and unstable SCFEs depending on the presenting symptoms and radiographic results. Stable SCFEs have statistically better outcomes.

There are three major types of therapies to prevent further slippage of the femoral head: spica cast immobilization, In situ fixation of the displaced femoral head with metallic pins or screws, and bone-peg epiphysiodesis. The most common procedure is the In situ fixation procedure and this is the procedure that this study will focus on. This procedure usually inserts a single metallic pin or screw through the central axis of the femoral head. If done properly, this procedure greatly reduces the chances of short term morbidities and long term complications.

In situ fixation has proved to be an effective treatment to prevent the further slippage of the femoral head. However, there are some possible complications to this procedure. First, further slippage is possible. But more worrisome complications are osteonecrosis or chondrolysis. Osteonecrosis is often caused by vascular disruption associated with the primary epiphyseal slip. But, if not noticed this can cause vast complications and issues later. Chondrolysis is an acute dissolution and degradation of the articular cartilage.

Methods: A retrospective, radiographic analysis of approximately 80 patients is in progress. Demographic data is collected for patients along with a clinical and radiographic analysis of the patient’s records. Information collected include types of injuries, details of the pinning procedures, hip angles, and other joint data, both immediately following injury/procedure and upon follow-up. One particular variable of interest is whether the type of screw/pin used during the SCFE pinning would make a difference in the progression of the SCFE at follow-up. A statistical analysis will occur following completion of data collection.

Results: A more detailed statistical analysis is underway and the established data will be presented at the symposium.

Conclusions: Conclusions are forthcoming following the detailed statistical analysis.
**Title:** THE EFFECT OF ASCITES FLUID AND DCR3 ON TUMOR ASSOCIATED MACROPHAGE

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**Department:** Department of Obstetrics and Gynecology, UW School of Medicine and Public Health

**Mentor(s):** Joseph Connor, MD

**Support:** Shapiro Summer Research Program and Department of Obstetrics and Gynecology

**Background:** DcR3, a member of the tumor necrosis factor (TNF) receptor superfamily, modulates genes expressed in tumor-associated macrophage (TAM). DcR3 is known to be concentrated and over-expressed in the ascites fluid of the peritoneal cavities of women with advanced ovarian cancer. The purpose of these experiments was to better define the interaction between DcR3 and TAM. We theorized that DcR3 had a supportive function for TAM.

**Methods:** Plastic adherence allows for crude enrichment for various cell types based on the amount of time the cells are given to adhere. In all samples, we used this technique to obtain an enriched macrophage population for primary cell cultures. Using a different time frame, this technique was also used to enrich for cancer cells from the patient samples. The primary cultures of enriched macrophage were either treated with autologous ascites fluid or recombinant DcR3, or were left untreated, as a control. The cultures incubated for one week with their respective treatment. The resulting cellular components of these cultures were defined by flow cytometry and cell culture media were analyzed for the presence and relative concentrations of DcR3 by ELISA.

**Results:** Six out of seven sample studies demonstrated that ascites fluid and DcR3 support the survival of TAM. The proportion of viable macrophage in the presence of either ascites fluid or DcR3 was increased by as much as 4.3 times that of unstimulated macrophage. Based on our ELISA data, the cultures that were enriched for macrophage yielded between 4 and 20 times the concentration of DcR3. In these cultures, DcR3 levels were inversely related to the proportion of tumor cells suggesting that the tumor cells are not the cells producing DcR3.

**Conclusions:** Our data indicate that the presence of DcR3 sustains the viability of TAM in the peritoneal cavities of women with ovarian cancer. In addition, these primary culture-based experiments suggest TAM, not tumor cells, are the dominant source of DcR3 in ovarian cancer.
Title: FARM TO SCHOOL IN WISCONSIN

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Mentor(s): Amy Meinen, MPH, RD, CD; Murray Katcher MD, PhD

Support: Shapiro Summer Research Program and Wisconsin Department of Health Services

Background: Farm to School programs are occurring throughout the nation. The purpose of these programs is to help connect local farmers with elementary, middle, and high schools. Farm to School will improve access to new markets for farmers and give students the opportunity to enjoy fresh healthier produce in schools. Finally, Farm to School programs teach students about nutrition, healthy eating, and agriculture. In order to ensure that legislation is passed in WI that can most effectively optimizes these programs, interventional planning needs to be conducted via a logic model, a policy brief, and an evaluation.

Methods: A logic model is formulated to ensure that all steps along the path to producing an efficient Farm to School programs in WI are addressed. The Department of Agriculture, Department of Public Instruction, Research Education Action Policy on Food Group, AmeriCorps, and the Department of Health Services were brought together to construct the logic model that focused on the health and economic outcomes of Farm to School. This logic model helped to organize a time line and reveal the order in which actions need to occur.

The progression of the logic model, which includes process and outcome objectives, is measured through evaluation criteria. Additionally, the logic model helps to maintain the focus of each aspect of the project by displaying the desired end result. The logic model emphasizes the needs of producers, school food service, and legislation in order to meet long term outcomes.

Evaluations for student consumption of locally grown foods, attitude change towards food, and knowledge change about nutrition and agriculture have been formulated to monitor developments. However, evaluation of food service staff, teachers, and farmers is also necessary in order to have a more thorough understanding of the impact of a Farm to School program on a community.

Moreover, it is quintessential to have political involvement to initiate new legislation in support of Farm to School in Wisconsin. To get legislators interested a policy brief has been produced that helps to explain the benefits and drawbacks of Farm to School, based on current research. The policy brief also gives information about the activities occurring at the federal level and in other states.

Conclusions: The importance of federal and state funding to help start Farm to School programs throughout the state is displayed in the logic model. Once the program has been established it should be self sustainable because it has economic, health, and educational benefits that should ensure its security. However, without the proper initiation, Farm to School programs will not be able to reach their potential.
Title: THE ROLE OF THE PREFRONTAL CORTEX IN “THEORY OF MIND”

Authors: Keisha Rogers, BS; Michael Koenigs, PhD

Department: Department of Psychiatry, UW School of Medicine and Public Health

Mentor(s): Michael Koenigs, PhD

Support: Shapiro Summer Research Program and Department of Psychiatry

Background: Being able to recognize and respond to others’ feeling and beliefs are crucial components of social behavior. Theory of mind can be described as the constellation of functions that involves making inferences about others’ mental states, including beliefs, intentions, and emotions. This ability to infer the mental states of others through recognition of facial emotions as well as actions in social situations was tested using the FEEST and Faux pas exams in patients with specific brain lesions. Areas of the prefrontal cortex, including the ventromedial and dorsolateral have been implicated in theory of mind abilities.

Methods: We compared the results of the FEEST and Faux pas exams of 7 patients with lesions that were localized to the ventromedial prefrontal cortex, 23 patients with lesions of the dorsolateral prefrontal cortex and 55 healthy controls. The FEEST exam is a computer based test that is used to detect the ability to recognize facial emotion and the Faux pas exam is a series of short stories containing a social faux pas.

Results: We found that patients with lesions in their ventromedial prefrontal cortex were more impaired in their ability to recognize facial emotions while the patients with lesions in their dorsolateral prefrontal cortex were impaired in faux pas recognition.

Conclusions: Both groups of prefrontal lesion patients displayed deficits in their theory of mind abilities. Future studies should further investigate the role of prefrontal cortex in social cognition.
MATERNAL OBESITY AT DELIVERY: A RISK FACTOR FOR NEWBORN IRON DEFICIENCY

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Support: Shapiro Summer Research Program, UW Cardiovascular Research Center, Meriter Foundation, 1ULIR025011 from the Clinical and Translational Science Award (CTSA) Program, UW Medical Education and Research Committee Wisconsin Community Partnership Program (Pamela Kling), Thrasher Research Fund, NIH T32HD049302 Health Disparities Research Scholar (Beth Fischer)

Background: Iron deficiency is the most common nutritional deficiency in the world, plaguing 7% of US infants. Research has indicated that obese adults and children are at increased risk for iron deficiency compared to non-obese counterparts. In addition, studies suggest that obesity is associated with higher rates of iron deficiency anemia due to the inflammatory changes associated with obesity interfering with iron absorption. Whether or not maternal obesity during pregnancy is related to newborn iron-status has yet to be examined. Thus, we hypothesized that maternal obesity would be associated with poorer newborn iron status.

Methods: 169 mothers and their term babies were recruited from the Meriter Hospital Birthing Center in Madison, WI, prior to hospital discharge. Mothers and infants with risk factors for iron deficiency were over sampled. Maternal characteristics including age, ethnicity, anemia, diabetes, pre-pregnancy and maternal delivery body mass index (BMI), and infant characteristics including sex and BMI were examined as possible predictors and/or covariates. Whole umbilical cord blood and reticulocyte-enriched ZnPP/H were examined as indices of iron deficiency. Enriched ZnPP/H was measured after isolating the youngest red cells.

Results: To examine group differences in maternal BMI, mothers with a BMI < 30 kg/m² were compared to mothers with a BMI > 30 kg/m². Initial Chi-square analyses indicated that BMI groups did not differ in regard to maternal ethnicity, anemia, or diabetes. A One-way Analysis of Variance (ANOVA) indicated that mothers with a BMI at delivery > 30 kg/m² gave birth to babies with a higher mean enriched ZnPP/H (M=131.6; SD=41.1) compared to mothers with a delivery BMI < 30 kg/m² (M=118.4; SD=42.5; F1, 168=5.1, p<.05), although the relationship was not linear.

Conclusions: Women with a BMI > 30 kg/m² have babies with higher ZnPP/H in reticulocytes, a measurement we previously found was sensitive to early iron deficiency. It is possible that pro-inflammatory changes interfere with maternal iron absorption and/or placental iron transport to the fetus during late pregnancy. Further research is required to investigate the connection between iron status and obesity, and inflammation.

References
Title: IMPROVING TIME AND ACCURACY OF ADIPOSE TISSUE SEGMENTATION

Authors: William Scheels, BS; A. H. Poonawalla, PhD; S. Reeder, MD, PhD

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Mentor(s): Scott Reeder MD, PhD

Support: Shapiro Summer Research Program and Department of Radiology

Background: The obesity epidemic the Western World is dictating the need for a better understanding of adipose tissue due to the increased number of patients with metabolic syndrome, type II diabetes mellitus, and related conditions. Visceral and subcutaneous adipose tissue (VAT and SCAT) play different roles in these conditions making it important to quantify the volume of adipose in these separate tissue compartments. Manual segmentation of VAT and SCAT has limited researchers to use small population sizes in studies because it is such a time consuming process with a propensity of operator bias, imperfect volume quantification, and reproducibility of T-1 weighted MR images. Development of a more semi-automated and fully automated segmentation process was a goal of our group in order to improve the accuracy and time necessary to quantify adipose tissue volume.

Methods: MRI images were captured in a single breath-hold from the dome of the liver to the pelvic floor using iterative decomposition with echo asymmetry and least-squares estimation (IDEAL). After images were reconstructed, both in-phase and fat only images were segmented using the SliceOmatic software package from TomoVision by using a variety of region of interest (ROI) tools. Initially, the subject’s arms were removed from both sets of images using the Region Growing tool, which segments areas based on seed points. SCAT from the in-phase image was then segmented using the Snake Mode, allowing for active contouring and propagation of the ROI to neighboring slices. VAT was then segmented using the watershed technique of Morpho Mode followed by the Brush Mode to segment the remainder of the ROIs that were not included in the initial segmentation sequence. Fat only images were analyzed differently by initially thresholding the entire image. The Brush Mode was used next do delineate the SCAT from VAT and finally the Region Growing tool was used to segment the remainder of the SCAT. SCAT and VAT volume could then be quantified in cm³.

Results: Speed and accuracy of segmentation was improved upon when the novel imaging technique of IDEAL was combined with reconstructed water and fat images and manual segmentation techniques. Stacks of fat only images, consisting of 32 images per stack, took on average 30 minutes to complete full segmentation. Stacks of in-phase images took upwards of 3-4 hours to complete.

Conclusions: Increasing the speed at which data sets are processed and analyzed when looking at SCAT and VAT will allow for more extensive studies regarding these two adipose compartments. With the image processing and the segmentation process improved we will ideally move forward with complete data sets from multiple subjects and compare the length of time it takes to go though such a process. Additionally, we will be using ImageJ, a free program issued by the NIH due to its universal accessibility and reproducibility.
Title: REDUCING INFANT MORTALITY DISPARITIES IN WISCONSIN: EXAMINING THE ROLE OF PLACE IN IMPROVING HEALTH OUTCOMES

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Mentor(s): Gloria E. Sarto, MD, PhD

Support: Shapiro Summer Research Program and UW Center for Women’s Health Research

Background: Overall, infant mortality rates (IMR) have decreased in the United States; however, the U.S. still ranks poorly, with an overall IMR of 6.78 deaths/1000 live births in 2004. It is theorized that this difference is due to the persistence of ethnic disparities between African American and White populations; 2004 data reports a black infant mortality rate (BIMR) of 13.6 deaths/1000 live births. Wisconsin is of great concern in particular, with a 2004 BIMR of 19.2 deaths/1000 live births. Comparing extremes, Racine, WI has seen a BIMR as high as 25 deaths/1000 live births, while Dane County, WI experienced a 70% decline in BIMR from 2002-2006, dropping from 19 to 6 deaths/1000 births. Poor birth outcomes have been attributed to many factors; therefore, this improvement warrants careful and widespread investigation into individual, clinical and community-level variables that may be involved. A three-year initiative has begun with the formation of the interdisciplinary Infant Mortality Coalition (IMC) to examine multiple facets of this issue, including the role of community assets (CA’s) in health outcomes.

Methods: In this portion of the study, internet searches of CA’s were conducted in Racine and Dane counties, and the data was compiled and coded into spreadsheets. Additional data was collected via one-on-one interviews with the local health departments and United Way staff. The resulting list of local resources was further assessed by community stakeholders in both counties. This data is being compiled within a schema of proximal supports (resources offering direct services to pregnant women and infants) and more distal supports which are organized under a conceptual framework made up of Dr. Lu’s Twelve-Point Plan to Reduce Racial Disparities in Birth Outcomes. They will be further assessed for adherence to evidence-based practice as well as their overall utilization and populations served. Finally, a geo-spatial analysis will be conducted, assessing accessibility and relevance to the targeted populations.

Results: At this time, results of the community asset analysis and mapping are still pending as data is still being collected in this three-year project.

Conclusions: This presentation addresses a three-month summer project that played a critical role in laying initial groundwork necessary for the gathering of data and building community support within Racine and Dane Counties for this project. Upon completion, the CA analysis will allow the IMC to consider the role of resources and accessibility within the contexts of place, community and life-course factors in determining birth outcomes.
Title: CHEMOTHERAPY-BASED TREATMENT IMPROVES SURVIVAL IN UTERINE CARCINOSARCOMA

Authors: James Spencer, BS; Stephen L. Rose MD

Department: Department of Obstetrics and Gynecology, UW School of Medicine and Public Health; UW Carbone Cancer Center

Mentor: Stephen L. Rose, MD

Support: Shapiro Summer Research Program and Department of Obstetrics and Gynecology

Background: The aims of this study were to compare overall survival and recurrence differences between uterine carcinosarcoma patients who received chemotherapy-based treatment compared to those who received adjuvant radiation alone or no adjuvant therapy.

Methods: Following institutional review board approval, we conducted a retrospective chart review of all women seen in consultation at the University of Wisconsin Carbone Comprehensive Cancer Center with the diagnosis of uterine carcinosarcoma between 1987 and 2009. Data were collected on patient age, diagnosis date, primary surgery, treatment details, dates of progression and death, and sites of first recurrence. Survival was calculated by subtracting date of diagnosis from the date of death or last contact for overall survival and from first recurrence for progression free survival. Survival curves were generated using the Kaplan-Meier analysis and compared using the log rank test statistic.

Results: Three women of the initial 75 were excluded from final analysis (2 for lack of follow up and 1 for multiple, concurrent cancers). Of the remaining 72 patients, 30 (42%) had stage I, 3 (4%) had stage II, 19 (26%) had stage III, and 20 (28%) had stage IV disease. Twenty-six (36%) patients received chemotherapy-based treatment: 20/26 (76%) received carboplatin and taxol, 2/26 (8%) received ifosfamide and cisplatin, 2/24 (8%) received platinum alone, 1 (4%) received adriamycin and platinum, and 1 (4%) received taxol alone. Overall 45 (63%) patients received radiation: 30/45 (67%) received radiation alone, and 15/45 (33%) received radiation with chemotherapy. Fifteen patients (21%) received no therapy. Overall survival and progression-free survival of the entire group, when adjusted for stage, revealed a significant advantage for those receiving chemotherapy-based treatment versus those receiving adjuvant radiation alone or no therapy ($p=0.005$ and $p=0.010$ respectively).

Conclusions: Our findings suggest that chemotherapy-based treatment improves overall and progression-free survival for women with uterine carcinosarcoma. Chemotherapy alone or given in addition to pelvic radiotherapy should be considered in the treatment of all stages of uterine carcinosarcoma, and should serve as the control arm for future clinical trials.
Title: BIOMECHANICAL COMPARISON BETWEEN TWO GUIDED GROWTH SYSTEMS

Authors: Andrea Stitgen, BS; K Garrels, MD; H Kobayashi PhD; R Vanderby, PhD; J McCarthy, MD; K Noonan, MD

Department: Department of Orthopedics and Rehabilitation, UW School of Medicine and Public Health

Mentor(s): Ken Noonan, MD

Support: Shapiro Summer Research Program, Department of Orthopedics and Rehabilitation

Background: The Orthofix 8-plate was the first tension band device developed for hemiepiphysiodesis; it has shown good results correcting angular deformities in children. Some recent reports have shown device failure, perhaps due to increased patient weight as seen in Blount’s disease. Other systems have become recently available; unfortunately follow-up is short and similar problems may arise. Our study purpose is to compare the strength to failure between 2 devices, the Biomet Peanut Plate (PP) and the Orthofix 8-Plate (8P).

Methods: To create failure, multiple attempts with several materials (Bovine bone and synthetic bone) were made via a single maximum pull; yet non-representative failure patterns ensued. Thus a model of cancellous and cortical bone was created using 30 pcf solid polyurethane foam and high density polyethylene, respectively. A 10.0 mm defect was created through the polyurethane foam and was spanned by one of the two Titanium plate and cannulated screw systems (6 PP and 6 8P). Under the assumption that device failure is caused by cyclical loading, each device underwent fatigue testing on a MTS Bionix machine with a 4 Hz micromotion of 5.0 mm at -500 N compression, and the # of cycles to failure was recorded.

Results: All devices failed at the screw shaft (18.5 mm from the screw head for PP and 18.0 for 8P [ns]); plates did not break under any circumstances. The mean number of cycles to failure for the Biomet device was 11,506 (SD = 2326), versus 7,532 (SD = 3212) for the Orthofix device. A student T-test was conducted, showing the statistically significant increase in fatigue life of the PP (35% stronger) vs. the 8P (p = 0.034).

Conclusions: This study reveals a 35% increase in strength in one titanium cannulated guided growth system over another. Long term clinical data will be required to see if this difference results in lower failure rates. Further work is ongoing to compare design variables such as solid screws or stainless steel material.
Title: EFFECT OF CHILD AND PARENT FACTORS ON PARTICIPATION IN PEDIATRIC CHRONIC CARE VISITS

Authors: Aistis Tumas; Matthew Swedlund; Elizabeth D. Cox, MD, PhD

Department: Department of Pediatrics, UW School of Medicine and Public Health

Mentor: Elizabeth D. Cox, MD, PhD

Support: Shapiro Summer Research Program and Department of Pediatrics

Purpose: Self-management is essential in pediatric chronic disease care. To improve the success of self-management, patients and their parents must develop skills in two key tasks in health care visits—building a relationship with healthcare providers and exchanging information. We quantitatively assessed how parent and child factors including gender, parent education, and child age affected participation in visits for 2 chronic diseases (asthma and diabetes).

Methods: Four subspecialty physicians (2 each in pediatric diabetes and asthma) were recruited. Children 9-16 years of age and their parents were recruited prior to their maintenance visit with participating physicians. We analyzed videos and sociodemographics from a total of 48 pediatric visits for diabetes (n=26) and asthma (n=22). Using the Roter Interaction Analysis Scheme, which assigns each speaker’s utterances into one of 34 mutually exclusive categories, videos were coded for relationship building, information giving, and information gathering. Interrater reliability was assessed by intraclass correlation coefficients (ICCs). Descriptive statistics and t-tests were used to analyze how participation in key tasks was associated with participants’ gender, parent education, and child age.

Results: Patients with diabetes were white (non-Hispanic), and predominantly accompanied by their mothers (84%). The child’s median age (interquartile range) was 12.4 years (10.2—14.6). Thirty-two percent of parents had at least a bachelor’s degree, and only 12% had not completed any college coursework. All ICCs exceed 0.70, indicating substantial to near perfect interrater agreement. The mean number (interquartile range) of relationship building utterances was 120 (100—136) for physicians, 64 (41—82) for parents, and 44 (15—56) for children. The mean number of information giving utterances was 112 (60—157) for physicians, 106 (67—135) for parents, and 65 (23—99) for children. The mean number of information gathering utterances was 40 (26—51) for physicians, 7 (3—11) for parents, and 3 (0—7) for children. Information gathering by the child increased significantly with age (p=0.005). No other significant associations were found between participation and child age, parent education level or parent gender.

Conclusion: In general, the parents of children receiving diabetes care at UW are highly educated, non-minority mothers. In these visits, relationship building by physicians and families is fairly balanced, but families provide more information than the physicians and rarely gather information. As expected, as children with diabetes mature, they perform more information gathering in their visits, yet parent information gathering remains stable across child age. Future work with asthma visit videos will examine the association of participation with child and parent factors as well as similarities and differences in participation in visits for pediatric diabetes and pediatric asthma.
Title: ALZHEIMER'S DISEASE: THE EFFECTS OF SIMVASTATIN ON CEREBRAL PERFUSION IN AT-RISK INDIVIDUALS

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Mentor(s): Cynthia Carlsson, MD, MS

Support: Medical Student Training in Aging Research (MSTAR) Program associated with the American Federation of Aging Research (AFAR). Grants NIA AG026752, 1UL1RR025011 and 5T35 AG026738-05.

Background: Preventive therapy for individuals at-risk for Alzheimer's disease (AD) is needed. Potential targets for prevention include cholesterol and cerebral perfusion. Simvastatin, a statin which crosses the blood-brain barrier, lowers cholesterol and has a direct influence on vasculature. No data exists on how statins influence the cerebral perfusion in asymptomatic adults at-risk for AD.

Methods: This randomized, controlled, double-blind clinical sub-study investigated the effects of 9 months of simvastatin on cerebral perfusion in middle-aged adults with a parental history of AD. The analysis focused on perfusion in the posterior cingulate (PC), which exhibits early hypoperfusion in the AD process. Fifty middle-aged adults with parental history of AD were recruited for this sub-study and were randomized in a 1:1 ratio to receive either simvastatin 80 mg daily vs. placebo. T*2–weighted MRI scans were performed at baseline and month 9.

Results: Participants (n = 47 with analyzable data, 53.9 ± 7.4 yrs, 67% women, 40.7% APOE4 carriers) had a parental history of AD. Twenty-one participants in this MRI sub-study received placebo and 26 received simvastatin. Increased baseline perfusion in bilateral PC was associated with female sex, lower systolic blood pressure and higher HDL (p ≤ 0.05). On perfusion MRI, there was no significant difference at month 9 in the change of cerebral blood flow of the right and left PC between treatment groups (p= 0.147).

Conclusions: In this sub-study analysis, individuals with a parental history of AD taking simvastatin for 9 months had no significant changes in PC perfusion compared to placebo. Further analyses of the complete data set are underway to better characterize the effects of simvastatin on other cerebral regions of interest relating to memory and learning. Larger randomized controlled trials with longer duration of statin therapy are warranted to see if statins increase regional cerebral blood flow and whether these changes correlate with cognitive function.
Title: SCOLIGAUGE AS A CLINICAL SCREENING TOOL FOR SCOLIOSIS PATIENTS

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Mentor(s): Paul A Anderson, MD

Support: Shapiro Summer Research Program and Department of Orthopedics and Rehabilitation

Background: An increasing number of medical applications are available for PDA’s and Smartphone’s. The utility of these applications depends on accuracy, consistency of readings, intra- and inter-rater reliability. The accuracy of measurements taken with the iPhone application Scoligauge needs to be proven valid and reliable before widespread use.

Methods: The iPhone was placed in a bi-axial materials testing machine and rotated clockwise and counterclockwise to simulate scoliosis. The iPhone was initially placed in a neutral alignment and then increasing degrees of tilt (backward and forward angulations) were applied. Correlation between the iPhone and known angulations were then examined and validated by comparing iPhone to a thorough and rigid protocol.

Results: The average of the differences, between actual and recorded measurements, was 1 degree or less when the unit was rotated in a clockwise direction with up to 15 degrees of forward or backward tilt. The average of the differences, between actual and recorded measurements, was 1 degree or less when the unit was rotated in a counterclockwise direction with up to a 20 degree forward or backward tilt.

Conclusions: The Scoligauge appears accurate to a level acceptable for use as a clinical application. The measurements were within the acceptable range for both the forward and backwards tilt of less than 15 degrees. Knowing that the measurements meet acceptable criteria, future directions will include clinical testing of intra-rater and inter-rater reliability in patients at University Hospitals and Clinics Pediatric Spine Clinic.
Background: Proximal row carpectomy (PRC), scaphoid excision with four-corner fusion, and wrist arthrodesis are all accepted procedures used to manage degenerative conditions of the wrist. Development of wrist arthritis is often a secondary consequence of structural changes of the carpal bones resulting in abnormal wrist mechanics. This is usually due to scapholunate dissociation, scaphoid fracture nonunion or rotary subluxation of the scaphoid, but can also be due to more chronic conditions such as Kienbock’s disease. The purpose of this study is to explore the long-term outcomes of proximal row carpectomy for patients with a minimum of 20-year follow-up who had the procedure for treatment of degenerative wrist conditions.

Methods: Forty-four living patients with a minimum of 20 years status post PRC were identified for inclusion in the study. To date, 14 patients have been contacted and have agreed to participate (12 of which have already been seen in clinic). Objective measurements included radiographic imaging of the affected wrist and measurement of wrist range of motion and grip strength. Patients were also asked to complete two surveys, the Disabilities of the Arm, Shoulder and Hand (DASH) and the Patient Rated Wrist Evaluation (PRWE), to determine subjective satisfaction with the procedure. All of this information was consolidated and quantified using a clinical outcomes scale as the primary outcome measurement.

Results: Six of the 44 patients (13.6%) who met the inclusion criteria had persistent wrist pain following the procedure and subsequently had wrist arthrodeses performed. These patients were not seen in clinic for this study as their PRC procedures had failed. Of the remaining 38 patients, 12 have already been seen, and all demonstrated favorable results on the clinical outcomes scale (11 “good” and one “fair”). The average DASH score was 9 (graded on a 0-100 scale with 100 demonstrating most disability). The PRWE produced results showing slightly more disability with an average score of 16 (similar 0-100 scale). Total arc of motion (TAM) and grip strength averaged 68% and 79% of the uninvolved hand, respectively. These same outcomes, compared to preoperative values, showed an average 25% improvement in TAM and a 300% improvement in grip strength.

Conclusions: This study remains in an ongoing recruitment phase to increase the power of the results. However, the current data seems to promote PRC as a reliable and effective method for wrist preservation as evidenced by considerable maintenance of wrist range of motion and grip strength as well as overall patient satisfaction with the procedure after an average 26-year follow-up.
Title: ISOLATION OF MULTIPOTENT CARDIAC PRECURSOR FLK-1+/CD31- CELLS FROM TRANSGENIC MOUSE EMBRYONIC STEM CELLS

Authors: Brent E. White, BS; Gary E. Lyons, PhD

Department: Department of Anatomy, UW School of Medicine and Public Health

Mentor: Gary E. Lyons, PhD

Support: Shapiro Summer Research Program and UW Cardiovascular Research Center

Purpose: Undifferentiated mouse embryonic stem (mES) cells and partially purified cardiac myocytes isolated from embryoid bodies (EBs) have shown an ability to repair post-myocardial infarction (MI) hearts. However, undifferentiated ESCs injected into the heart are capable of forming teratomas. On the other hand, fully mature, adult ventricular myocytes, although incapable of forming tumors, have minimal ability to engraft, divide and repair myocardium. Therefore we desired to isolate a multipotent progenitor cell capable of becoming all types of cardiac tissue without forming teratomas. Developmentally, cardiac muscle and blood are of mesodermal origin. Flk-1 (fetal liver kinase) is a cell surface receptor and an early mesodermal marker highlighting the earliest stage of the hematopoietic and vascular lineages. We utilized an MLC2V-ECFP transgenic mouse ES cell line which expresses an inserted ECFP gene under the control of the myosin light chain 2 ventricular promoter. Our goal was to isolate a cell population that was Flk-1 positive but negative for CD31, an endothelial marker. To accomplish this, we used Fluorescence Activated Cell Sorting (FACS) to separate cells that are Flk-1 positive but CD31 negative to produce a mouse ESC-derived cell population that would be optimal for engraftment and proliferation without teratoma formation.

Methods: The mES cells were cultured and maintained according to standard methods. Cells were allowed to differentiate for 3, 4, and 5 days using the hanging drop method, and the EBs that formed were harvested. EBs were plated onto 6 well plates coated with 0.1% gelatin and the number of beating areas seen under a microscope were counted. Plated EBs were dissociated with 0.25% trypsin-0.04 mM EDTA for 10 min at 37°C and collected. These cells were analyzed on a FACSCalibur flow cytometer to determine the percentage of ECFP+ cells. EBs from hanging drops were also harvested, dissociated with trypsin, and incubated with Flk-1-phycocerythrin (PE) and CD31-fluorescein isothiocyanate (FITC) antibodies. These samples were then fixed with 2% paraformaldehyde and analyzed on a FACSCalibur flow cytometer to determine which day yielded the highest percentage of Flk-1+/CD31- cells. Live cells from day 5 EBs stained with Flk-1-PE and CD31-FITC antibodies were sorted by FACS to isolate Flk-1+/CD31- cells, and these cells were plated onto mouse embryonic fibroblast feeder layer cells.

Results: Day 5 EBs that were plated yielded the highest number of beating areas. The ECFP+ signal was too weak to detect so the percentage of ventricular myocytes could not be determined. Day 5 EBs yielded the highest percentage of Flk-1+/CD31- cells. We sorted and cultured Flk-1+/CD31- cells from day 5 EBs. Antibody staining of these cells revealed that after several passages, the cells remained Flk1+ and CD31-. Further staining revealed that these cells appear to have an intermediate cell phenotype that expresses both pluripotency and mesodermal markers.

Conclusions: We have successfully isolated and maintained mouse ES cells that are Flk-1+ and CD31-. We expect these cells to yield a higher percentage of cardiomyocytes and to be more effective in regenerating damaged cardiac tissue in future experiments.
Title: TARGETING THE MAPK PATHWAY IN A MOUSE MODEL OF DILATED CARDIOMYOPATHY

Authors: Alex M Witek, BS; Timothy A Hacker, PhD; Ravi Balijepalli, PhD; Matthew R Wolff, MD

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Mentor(s): Timothy A Hacker, PhD

Support: Shapiro Summer Research Program and UW Cardiovascular Research Center

Background: Mutations in the LMNA gene have been associated with several diseases, including dilated cardiomyopathy with conduction system disease (DCM-CD1). While the mechanisms by which LMNA mutations cause DCM-CD1 are not known, the MAPK signaling pathway has been implicated in disease progression. A mouse model with an N195K LMNA mutation has been developed, which exhibits decreased lifespan, dilated heart chambers, thinner chamber walls, conduction system abnormalities, and abnormal structure of nuclei and sarcomeres. We tested the hypothesis that administration of MAPK inhibitors in this model would decrease activation of the MAPK pathway and slow the progression of dilated cardiomyopathy.

Methods: Mice were treated for 4 weeks starting at 21 days old with the JNK inhibitor JNK-II (IP 5x week). Echocardiography was performed on all mice at baseline (21 days old) and after 4 weeks and used to measure LV chamber diameter, wall thickness, and flow velocities through the mitral valve and in the ascending aorta. These values were used to calculate LV mass and ejection fraction. A mouse cDNA array (Nimblegen) was performed to compare gene expression between wild-type and mutant mice.

Results: Four weeks of treatment with JNK-II resulted in a decrease in the ratio of LV mass to body mass in the mutant JNK-II treatment group (4.81 mg/g; SD 0.78 mg/g), compared to mutant controls (5.59 mg/g; SD 1.32 mg/g; p=0.21). The same treatment resulted in no significant difference in treated wild-type mice versus wild-type controls (p=0.69). Treatment did not alter cardiac function in either mutant or wild-type mice. The RNA expression analysis identified several genes with a large fold-change in expression levels between mutant and wild-type mice, including members of MAPK pathways, myofibril components, and ion channels.

Conclusions: The observed decrease in LV mass with JNK-II treatment suggests that the treatment may alter signaling or remodeling mechanisms involved in cardiac hypertrophy; however, this trend was only weakly statistically significant, possibly due to small sample sizes. Continued study with additional mice is necessary to further investigate the significance of the observed trend and may also help identify other significant trends in myocardial structure or performance. The genes identified as being significantly up- or down-regulated in the mutant mice represent potential therapeutic targets for future studies.
Title: PREPREGNANCY BMI AND NUTRITIONAL CARE DO NOT CONTRIBUTE TO DECREASE IN DANE COUNTY’S BLACK INFANT MORTALITY

Authors: Carley Zeal, BS; Laura Berghahn, MD; Amanda Schmehill, MD; Murray Katcher, MD

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Mentor(s): Laura Berghahn, MD; Gloria E Sarto, MD, PhD

Support: Shapiro Summer Research Program and UW Center for Women’s Health Research

Background: Between 1997 and 2007, a decrease in the black infant mortality rate (BIMR) was observed in Dane county, closing the disparity between black and white IMR’s. The survival rate of babies weighing less than 1500 grams as well as decreased premature deliveries were found to be the main contributors. Malnourished and underweight mothers have been identified as higher risk for preterm delivery. Studies also show increased neonatal mortality and assisted deliveries among overweight and obese women. Studies have shown that counseling on nutrition and lifestyle decreased pregnancy weight gain and therefore behaviors, and the AGOG recommends such treatment. Given this information and the current obesity epidemic it is of interest whether a change in nutritional care of women may contribute to the decreased BIMR.

Methods: Charts of African American women delivering babies in Madison in 1997 and 2007 were investigated. Prepregnancy BMI’s were calculated and record of dietary referral or counseling was noted. Women were classified by year as underweight (BMI<19), overweight (25<BMI<30), and obese (BMI >30). Percentages receiving dietary referral or counseling were compared.

Results: Results show no significant difference in BMI’s between 1997 and 2007. There was also no significant difference in “diet discussed” marked on record. A significant decrease in nutritionist referrals was noted. Other results include increased likelihood of cesarean section and gestational diabetes among overweight and obese women.

Conclusions: Given the decrease in nutritional referrals in 2007, it is thought that nutritional care does not contribute to the decrease in BIMR, though other studies are investigating possible social factors contributing to the BIMR. This study identified a need for improvement in nutritional care of pregnant women in Dane County.
Title: IMPROVING CARDIAC SURGICAL CARE: A WORK SYSTEMS APPROACH

Authors: Robert Zemple, MA; Ashley Eggman, MS; Renaldo Blocker, MS

Department: Department of Surgery, Division of Cardiothoracic Surgery, UW School of Medicine and Public Health

Mentor(s): Niloo Edwards, MD; Douglas Wiegmann, PhD

Support: Shapiro Summer Research Program and UW Institute for Clinical and Translational Research grant (Wiegmann PI)

Background: Over the past 50 years, significant improvements in the number of patients who survive and fully recover from open heart surgery have occurred. The average complication rate for most heart surgeries is now less than 5%. Nevertheless, considerable variability in surgical outcomes still exists across institutions and individual surgeons, and surgical errors that significantly impact patient safety continue to be reported. Focusing only on individual skill of the surgeon assumes that surgeons and other members of the surgical team will perform highly and uniformly, regardless of the variable working conditions. Alternatively, a work systems approach recognizes that surgical skill alone is not sufficient to determine outcomes because the process of delivering surgical care involves several interdependent variables, which vary across hospitals, operating rooms or surgical cases, and most of which are not normally under the control of the surgical team. Our long-term goal, therefore, is to further improve cardiac surgical care by enhancing or re-engineering the surgical care process. The immediate goal of this pilot project is to develop a methodology for reliably identifying work system factors in the operating room that negatively impact surgical performance.

Methods and Results: Currently, no tool exists for documenting dynamic work system factors, surgical team behaviors, or outcome variables in real time. Measurement instruments that do exist focus on subjective rating of the work process or team performance (Malec et. al., 2007). Therefore, as part of this project, we developed and utilized a Tablet PC data collection tool that helped standardize observations across observers and automatically time stamp entries. The tool was designed to capture the onset/offset of the event, the type of event, a description of the event and the disruptive nature and impact of the event on surgical performance. As in our previous studies within other healthcare settings, our tool provides more elaborate and reliable data than basic unstructured observations. We used multiple observers to code selected cases in order to establish reliability of our data collection process with the goal of reaching 80% agreement between a pair of observers. The observational team was comprised of a medical student who had received training in human factors, and two human factor graduate students who received training in observing medical/surgical teams. In this study, we conducted 26 observations over a five-month period. In thirteen of the observation, two team members observed from the same location and in the other thirteen cases the observers observed from different locations within the operation room. The surgical cases last at least five hours and were conducted in multiple operating rooms within the hospital and with mixed surgical teams. Results revealed that observers were roughly 87% reliable in identifying work system factors that disrupted surgical flow (an unnecessary pause in task) when standing in the same location. However, when standing in different locations, reliability dropped to 67% on noting similar events.

Conclusions: The research presented describes the development of a Tablet PC tool to reliably identify work system factors in the operating room that negatively impact surgical performance. However, locations of observers need to be considered when using the tool for evaluating future interventions for improving patient safety.
**Title:** SEXUALLY TRANSMITTED DISEASE SCREENING AND IMPROVED BIRTH OUTCOMES AMONG AFRICAN AMERICANS IN DANE COUNTY

**Authors:** Qi Zhang, BS; Gloria Sarto, MD, PhD; Laura Berghahn, MD; Murray Katcher, MD; Carley Zeal, BS; Songwon Seo, MS

**Department:** UW Center for Women's Health Research; Department of Obstetrics and Gynecology, UW School of Medicine and Public Health

**Mentor(s):** Gloria Sarto, MD, PhD; Laura Berghahn, MD; Murray Katcher, MD

**Support:** Shapiro Summer Research Program

**Background:** Dane County has experienced a decrease in black infant mortality rate (BIMR) by approximately 70% from 19.4 deaths per 1000 live births during 1990-2001 to 6.4 in 2002-2007. Improvements in birth outcome such as a decline in premature births (< 37 weeks gestation) may be a critical factor. Gonorrhea, bacterial vaginosis (BV) and urinary tract infections (UTI) during pregnancy have all been associated with pre-term pre-labor rupture of membranes (PPROM), low birth-weight, and or premature deliveries. The goal of this study is to explore whether increased sexually transmitted infections (STI) and UTI screening during pregnancy in the last 10 years has led to improved African American birth outcomes in Dane County.

**Methods:** We examined labor summaries and prenatal records of African Americans residing in Dane County of southern Wisconsin who gave birth in 1997 (N=114) and 2007 (N=248). Data was collected from the medical records of one of the two Dane County hospitals providing obstetric services. We compared the rates of screening, positive tests and tests of cure for gonorrhea, chlamydia, UTI, BV, syphilis, and HIV documented in the prenatal care records. Demographic variables included age, gravida/parity, marital status, provider of prenatal care, gestational age at first prenatal visit, gestational age at delivery, mode of delivery and insurance type.

**Results:** Of those who delivered in 1997, 55.26% had their urine cultured for UTIs compared to 90.32% in 2007, p-value < 0.0001. In 1997, 31.75% of the urine cultures collected were positive for bacterial growth, compared to 16.07% in 2007, p-value = 0.01. VDRL/RPR titers for syphilis were drawn from 92.98% in 1997, compared to 97.58% in 2007, p-value = 0.04. There was no difference in positive VDRL/RPR titers. HIV screens were performed on 70.18% in 1997 versus 79.84% in 2007, p-value = 0.05. There was no difference in HIV positive screens between 1997 and 2007. There was no statistical difference in the amount of gonorrhea and chlamydia screens, or the percentage of positive BV infections between the two years.

**Conclusions:** We found that in 2007, there was increased documentation of pre-partum screening for certain STIs such as HIV and syphilis, as well as for UTI among African Americans in Dane County compared to 1997. There has also been a significant decrease in the number of documented UTI during pregnancy in 2007 compared to 1997. Increased vigilance in STI screening during prenatal care could have contributed to a decline in premature births, thus improving birth outcomes for African Americans in Dane Country over the last decade. However, the decline in premature births and decrease in BIMR is likely multifactorial, an outcome of social and clinical interventions in prenatal care.
Title: INTENSIVE INSULIN THERAPY FOR THE PREVENTION OF INFECTION IN THE CRITICALLY ILL: A META-ANALYSIS OF PROSPECTIVE, RANDOMIZED TRIALS

Authors: Matthew Ziegler; Germana Silva, MD; Cybele Abad, MD; Nasia Safdar, MD, MS

Department: Department of Medicine, UW School of Medicine and Public Health

Mentor(s): Nasia Safdar, MD, MS

Support: Shapiro Summer Research Program and Department of Medicine

Background: Hyperglycemia has been shown to increase rates of infection and mortality in patients with and without diabetes. However, studies examining the role of intensive insulin therapy (IIT) in the critically ill have reached conflicting conclusions. We undertook a meta-analysis to determine the impact of IIT on the incidence of infection.

Methods: Data Sources: we searched 15 international databases including MEDLINE, EMBASE, and CENTRAL from database inception until 5/28/2009 using the terms “intensive insulin therapy” and nine synonyms. Study Selection: prospective randomized controlled trial of critical care or surgical patients were included, where IIT was compared with standard care and at least one type of infection was reported. IIT was defined as a target blood glucose concentration of 8.3 mmol/L or lower. Data Extraction: we extracted general study characteristics, incidence of infection, mortality, and hypoglycemia. Subgroups of medical (<50% surgical patients) and surgical (>50% surgical, perioperative or intraoperative patients) patients were performed for primary endpoints. Infections were analyzed as composite infection, pneumonia, wound, urinary tract, and sepsis. Data Synthesis: 20 studies including one unpublished trial were included in the analysis. Data were analyzed using random-effects model. Heterogeneity was measured with a Cochran Q statistic and I².

Results: Primary endpoints: composite infection was significantly reduced in the IIT group (20 studies, pooled RR=0.80 CI=0.71, 0.90; P=0.0002) with moderate heterogeneity (I²=53.5%), as shown in the figure. Subgroup group analysis of composite infection showed significant reduction in the surgical subgroup (11 studies, pooled RR=0.66, CI=0.57, 0.76; P<0.001) but non-significant difference in the medical subgroup. Sepsis overall was not significantly reduced with IIT. However, subgroup analysis of sepsis showed significant reduction in the surgical subgroup with no heterogeneity (8 studies, pooled RR=0.64, CI=0.48, 0.85; P=0.0024) but non-significant difference in the medical subgroup. Among the subgroups of infections we examined, only pneumonia was significantly reduced (10 studies, RR=0.84, CI=0.72, 0.97, P=0.0212). There was a four-fold higher risk of hypoglycemia; however heterogeneity was high (I² =99.4%).

Conclusions: We found that IIT is associated with a significant reduction in overall infection. Subgroup analysis revealed reduction in combined infection and sepsis in the surgical subgroup but not in the medical subgroup. The risk of hypoglycemia must be taken into consideration when employing IIT for reducing infection.
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