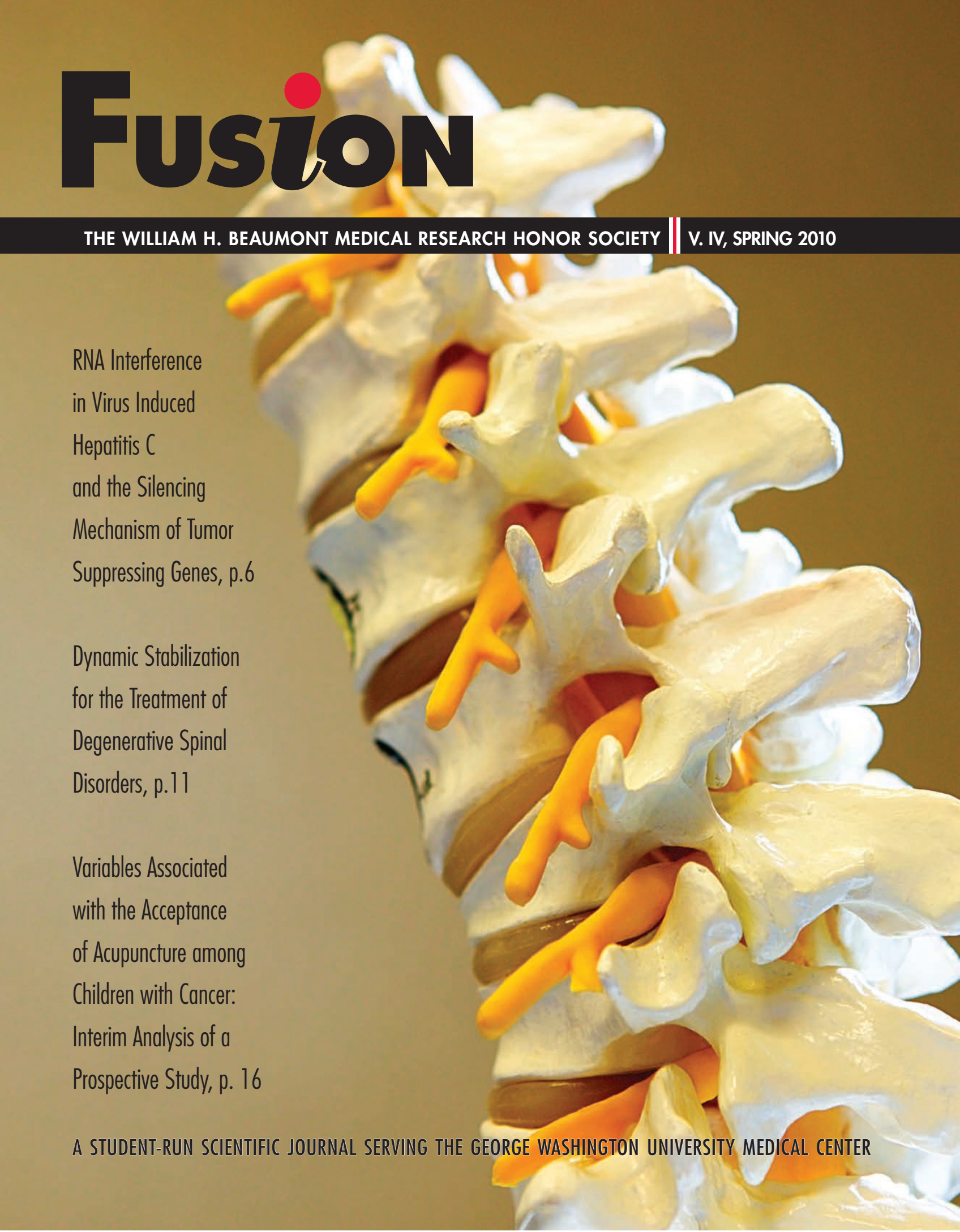
Fusion

THE WILLIAM H. BEAUMONT MEDICAL RESEARCH HONOR SOCIETY | V. IV, SPRING 2010



A STUDENT-RUN SCIENTIFIC JOURNAL SERVING THE GEORGE WASHINGTON UNIVERSITY MEDICAL CENTER

about the society. . .

BEAUMONT LEADERS

Back row from left: Gena Gora, Jay Bhatt, Waleed Kurtom, Junaid Shams, and Neha Jakhete. Front row from left: Kate Serdy, Sonia Samtani, and Allison Spitzer. Not pictured: Sheliza Lalani.

The William H. Beaumont Medical Research Honor Society is a research society of medical students that was established in 1935 to honor Dr. William H. Beaumont (1785–1853), a U.S. Army surgeon known as the "father of gastric physiology" for his groundbreaking research on human digestion. The organization seeks to foster a continuing interest in research and to promote the value of research in the practice of medicine. As a part of this mission, the Society integrates current research topics into the curriculum; publishes Fusion, a scientific journal showcasing GW School of Medicine and Health Sciences student research; makes available information on research opportunities throughout the area, including the William T. Gill Summer Fellowship for GW medical students; and highlights student and faculty research accomplishments at the annual GW Medical Center Research Day.

inside this issue. . .

VOLUME IV SPRING 2010

Fusion **is a publication of The George Washington University Medical Center's William H. Beaumont Medical Research Honor Society.**

This research journal is published by students in collaboration with the Office of the Dean; Office of Health Research, Compliance and Technology Transfer; and Medical Center Communications and Marketing.

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Fusion

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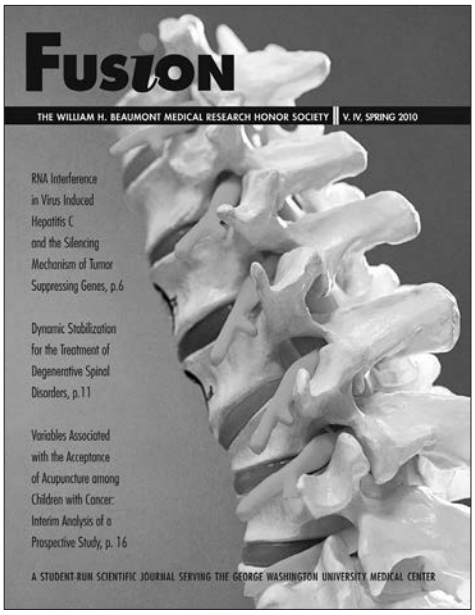

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HEALTH POLICY ABSTRACTS

from the editors. . .

As your co-Presidents for The William H. Beaumont Medical Research Honor Society, we are proud to present you with the fourth edition of *Fusion*, GW School of Medicine and Health Science's (SMHS) entirely student-run research journal, featuring basic science, clinical, and health policy research conducted by GW medical students. The articles span a wide variety of clinical specialties and scientific disciplines, from genetics and orthopaedic surgery to neurosurgery to cardiology to cancer research and therapy. This year we limited submissions to student research conducted during medical school that led to quantifiable scientific results, which we believe enhances the quality of *Fusion* as a student scientific journal and as a reflection of the significant research accomplishments of GW medical students. This is an exciting time to be conducting research at SMHS — with GW Medical Center (GWUMC) receiving major grants such as the Department of Microbiology, Immunology and Tropical Medicine's recent $15 million grant from National Institutes of Health (NIH) — and we are excited to be representing student research at SMHS through the Beaumont Society.

We are pleased to have continued our Journal Club meetings this year, and have improved the format of Journal Club by taking advantage of a rich resource immediately at our fingertips — recruiting leading faculty members and specialists in their fields to moderate our discussions, providing valuable clinical and seasoned perspectives on key topics. Stay tuned for more discussions of current research articles this spring, led by our M.S.I Beaumont members!

One frequently asked question is, "What is Beaumont anyway?" The standard answer is that Beaumont is a student-run society for students with an enthusiasm for, and an interest in, research. We provide students with a forum to discuss current and past landmark scientific studies through our Journal Club, an outlet to share their research findings with their peers and the GWUMC community through publication in *Fusion* and poster presentations at Research Day, and a resource to learn about research opportunities available at GW, the NIH, and across the United States. The real answer, however, is that Beaumont is whatever you want it to be — we are always open to new ideas and suggestions and we invite you to submit yours to us at *gwbeaumont@gmail.com*.

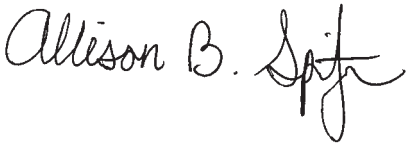
We would like to give our special thanks to Dean James Scott, M.D.; Dean Scott Schroth, M.D.; and Associate Vice President Anne Hirshfield, Ph.D., for their dedicated guidance and support as well as their innovative suggestions for the improvement of the Beaumont Society, to our past (and future) Journal Club faculty moderators, Lakhmir Chawla, M.D., and Lisa Martin, M.D., as well as all of the faculty who mentored our peers during their research projects, as well as to Thomas Kohout for his hard work, patience, and positive attitude while assembling this year's journal and the student authors and the editors of *Fusion* for all of their hard work throughout the editing process. Our final thanks go to Beaumont Society Vice-President and fellow Fusion Editor-in-Chief, Sonia Samtani, for her work ethic, enthusiasm and spirit during this entire process.

Thank you all and we hope you, the GWUMC community, enjoys Research Day and *Fusion* 2010!

Sincerely,

Kate Serdy, M.S.II

Allison Spitzer, M.S.II

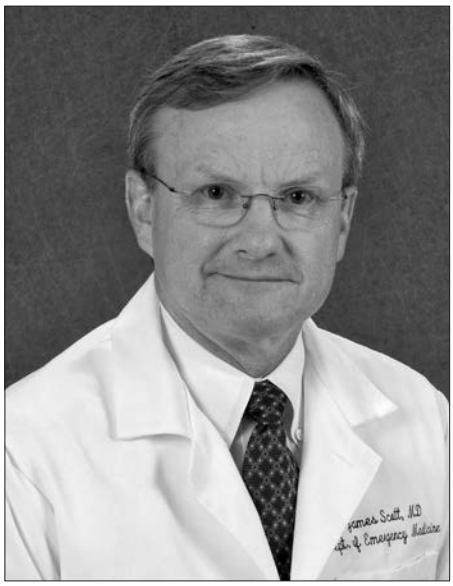


Co-Presidents of the William Beaumont Society

Kate M. Serdy, M.S.II

Allison B. Spitzer, M.S.II

from the dean's office. . .



Congratulations to the students of The George Washington University on the research featured in this fourth edition of *Fusion*. A special thanks to Allison Spitzer, Kate Pickoff and Sonia Samtani as well as the rest of the William H. Beaumont Medical Research Honor Society for all of your hard work to make this journal possible. I would also like to recognize Dr. Anne N. Hirshfield who serves as the faculty advisor to the Beaumont Society for the encouragement she gives to our students working in research. I would also acknowledge the importance of the enthusiasm and dedication of our scientific investigators. Finally, I'd like to acknowledge the staff in the Office of Student Opportunities and the generous supporters of that office who continue to make medical research attainable for many of our students.

In every way research is growing at the GW School of Medicine and Health Sciences and Children's National Medical Center. We have major new grants in cancer, quality outcomes, neuroscience and tropical diseases. Our residents have presented and published more papers than ever and there are a myriad of opportunities for research activities by students. Scientific discovery and the creation of new knowledge is the hallmark of any School of Medicine and Health Science and with this publication we recognize the vital and stimulating role that our students have in our research accomplishments.

Fusion is a student-run publication that showcases the abilities of the students of the School of Medicine and Health Sciences. I take great pride in the achievements of our students and hope you are as impressed with their work as I am.

James L. Scott, M.D.
Dean, School of Medicine and Health Sciences,
Professor of Emergency Medicine

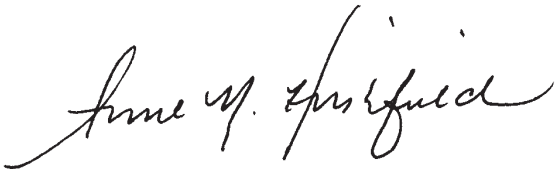
from the research office. . .

In collaboration with the students of GW's William Beaumont Medical Research Honor Society, I am proud to present the 2010 edition of *Fusion*, the fourth volume of a publication created by the members of this prestigious honor society. The William H. Beaumont Medical Research Honor Society was established at the GW School of Medicine in 1935 to promote student research.

The officers of the Society wanted to communicate the excitement and value of their experiences to you while carrying out research rotations, summer projects and activities that are preparing them for their medical careers. The previous editions of *Fusion* have been received with enthusiasm and, as a result, you, the wider audience have reaped the benefits from perusing the pages of this journal.

Fusion is an entirely student run publication that highlights the students' abilities as promising doctors and researchers. In addition, we salute the faculty advisors and all those who have mentored and assisted in any way to make this publication a reality. We also need to acknowledge the W.T. Gill Endowment, which on a yearly basis, provides stipends to eligible students to gain valuable experience in research during the summer months.

As our health care system evolves and as new discoveries in medicine become evident, our students' efforts now will prepare them for the challenges that lie ahead. I am honored to serve as the society's faculty advisor and am happy to support these gifted students in their research endeavors.



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RNA Interference in Virus Induced Hepatitis C and the Silencing Mechanism of Tumor Suppressing Genes

Hepatitis C, caused by the Hepatitis C Virus (HCV), is an infectious disease affecting the liver. Although asymptomatic upon acute infection, chronic infection can lead to liver cirrhosis and potential liver failure.[1] With no vaccine currently available, an estimated 170 million people are chronically infected worldwide with 3–4 million people becoming newly infected each year.[2]

Upon infection, HCV induces precursor microRNA (miRNA) to develop into mature miRNA by interaction with the DICER protein, an endoribonuclease that cleaves pre-miRNA into short, miRNA fragments. The mature miRNA, a double-stranded RNA molecule of 21–23 nucleotides, interacts with Ago proteins which initiate the selection of the complementary guide strand and catalyze its binding to target mRNA of hepatocyte tumor suppressor genes (TSGs).[3] This multiprotein complex of Ago proteins and miRNA is known as a RNA-induced silencing complex (RISC).[4] RISC disrupts the tumor suppressor genes' level of expression via translational function repression.[5] The down regulation of TSGs leads to the uncontrolled growth of hepatocytes and subsequent hepatocellular cirrhosis and potential carcinoma. However, it is unclear exactly where and how RISC is formed within the cell as well as how the activated complex locates the mRNA targets.

RNA binding proteins TRBP and HuR are integral components in the formation of RISC. More specifically, these proteins are involved in the recruitment of other proteins such as Ago to the pre-miRNA/dicer complex.[5] The purpose of our study was to discover the cellular localization of where these proteins originate and function within HCV infected cells. Such knowledge would provide us with more insight as to where RISC is formed and the mechanisms by which it interferes with gene expression.

Wild type hepatocytes (used as standards) and mutant hepatocytes infected with HCV were grown separately and subsequently transfected with FLAG-tag TRBP and HuR proteins to increase their relative intracellular concentrations. Following incubation, a cellular fractionation separated the cytoplasmic, nuclear, and nucleolar components of the cells. A western blot using an anti-FLAG antibody was performed to assess the location in which normal and mutant cells were using TRBP and HuR for their biochemical processes. Following several trials, our results indicated that in both wild type and HCV infected cells, varying HuR concentrations were found throughout the cellular compartments. However, higher TRBP concentrations were encountered in the nucleolus of infected cells when compared to normal cells. Our hypothesis of RNA binding proteins, specifically TRBP, demonstrating increased activity in specific regions of the cell during infection was substantiated. The variability in HuR, however, highlights the complexity of culturing, transfecting, and fractionating viable hepatocytes. Procedural and analytical modifications to achieve reproducible results are currently being developed. Nevertheless, the preliminary results of this project suggest that TRBP resides mainly in the nucleolus upon infection and therefore, RISC formation and interference may occur in proximal vicinity. However, more research is needed to determine the roles these proteins play in RNA interference and the cellular regions they are most active in. Such information can help elucidate the complex biochemical processes involved in advancing Hepatitis C infection from an acute to chronic stage. Moreover, by understanding the specific interactions between proteins along the gene silencing cascade, steps can potentially be targeted and therapeutically knocked down to disrupt disease progression.

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Ethanol-Induced Apoptosis in Cultured Cells is Mediated by the Endoplasmic Reticulum

Andreea Balan, M.S.III
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Alcohol abuse, known for promoting cell death in the liver and nervous system, is a major public health concern.[1–2] Despite significant morbidity and mortality resulting from alcohol, its precise cellular mechanism remains unknown. The present study investigated the sub-cellular mechanism of ethanol toxicity, specifically whether ethanol-induced apoptosis involves the mitochondria or endoplasmic reticulum (ER).

Ethanol induces apoptosis in cells via a caspase-dependent mechanism.[3] Control of caspase activity, and thus apoptosis, is directly modulated by the Bcl-2 family of proteins, which includes both pro- and anti-apoptotic members.[4] Anti-apoptotic Bcl-2 protects cells from apoptosis by inhibiting caspase activation, and Bcl-2 is known to be localized to mitochondria and the ER.[5] Prior *in vivo* studies have shown that overexpression of wildtype Bcl-2 is protective against ethanol toxicity,but it is not known whether protection is mediated through mitochondrial Bcl-2 or ER Bcl-2.[6]

Chinese hamster ovary cells (CHO695) were transiently transfected with cDNA constructs encoding GFP:Bcl-2 wildtype, GFP:Bcl-2 MAOB (mitochondria targeted) or GFP:Bcl-2 Cb5 (ER targeted) in order to determine the subcellular mechanism of rescue from ethanol toxicity by Bcl-2. MTT assay was used to measure cell viability in response to a range of ethanol concentrations at different time points in naïve CHO695 cells or in CHO695 cells overexpressing wildtype or organelle-targeted Bcl-2. Cells expressing GFP alone served as control. Ethanol treatments of 1 M and 2.5 M caused significant cell death at five, 10 and 24 hours. Wildtype Bcl-2 provided significant rescue for CHO695 cells treated with 1 M ethanol at the most severe (24 hour) time point, but did not rescue from toxicity at 2.5 M ethanol. However, ER-targeted Bcl-2 provided significant and robust rescue at 1 M and 2.5 M. Interestingly, mitochondrial-targeted Bcl-2 offered no significant protection at any ethanol concentration, suggesting the ER is central to the ethanol apoptosis mechanism.

In order to confirm these transfection data, and determine the sub-cellular mechanism of rescue from ethanol toxicity, we employed a peptide inhibitor approach to investigate whether mitochondria or ER caspases were responsible for ethanol-induced apoptosis. Caspase-9 and caspase-12 are known to be downstream of mitochondria and endoplasmic reticulum, respectively. CHO695 cells were treated with either a pan-caspase inhibitor, a caspase-9 inhibitor or a caspase-12 inhibitor and then treated with 1.5 M ethanol. MTT cell viability assay was used to measure cell viability in response to ethanol treatment. Untreated cells served as a control. Treatment with the pan-caspase inhibitor provided significant rescue from ethanol toxicity. Inhibition of caspase-12 conferred significant protection from ethanol toxicity as well, while inhibition of caspase-9 did not provide significant rescue. These findings confirm our transfection data and demonstrate a central role for the ER in ethanol toxicity.

In conclusion, the present study indicates that Bcl-2's amelioration of ethanol toxicity is most likely mediated through the ER. Therefore, ethanol-induced apoptosis does not occur via a mitochondrial stress pathway and caspase-9 activation but rather through an ER stress pathway and subsequent caspase-12 activation. Future work should clarify the role of the ER in ethanol toxicity.

APOPTOSIS

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APOPTOSIS

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Kate M. Serdy, M.S.II
Research Track
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Fibroblast Growth Factor Receptor (FGFR) Trafficking is Modulated by Shisa

The requirement for mesenchymal fibroblast growth factor 10 (FGF10) signaling in gastrointestinal development has been previously demonstrated. Through epithelial FGF receptor 2-IIIb (FGFR2b), a tyrosine kinase transmembrane receptor, FGF10 facilitates the epithelial-mesenchymal interaction and is necessary for proper development of the gut from embryonic days E11.5-E15.5 in mice. This mechanism is exhibited in FGF10 or FGFR2b null mice that demonstrate intestinal atresia in similar phenotypes. Defining the means by which the expression of FGF10 or FGFR2b are regulated may contribute to a more complete understanding of the development of intestinal atresia.

Before cell surface expression, FGFR2b must undergo post-translational glycosylation. This modification occurs in the Golgi complex after the receptor is released from the endoplasmic reticulum (ER). Shisa is an ER retention molecule that is known to bind with FGFR2b, and it has been postulated that Shisa may modulate the membrane availability of FGFR2b by regulating the movement of the receptor from the ER to the Golgi complex for glycosylation. Shisa is known to bind with FGFR2b in the ER, but it has not been shown to be present in the Golgi complex.

To demonstrate Shisa expression, HeLa cells were transfected with mShisa-GFP and mCherry-ER (as an ER marker). Confocal microscopy was used to evaluate co-localization. Immunostaining was performed with affinity-purified cation-independent mannose-6-

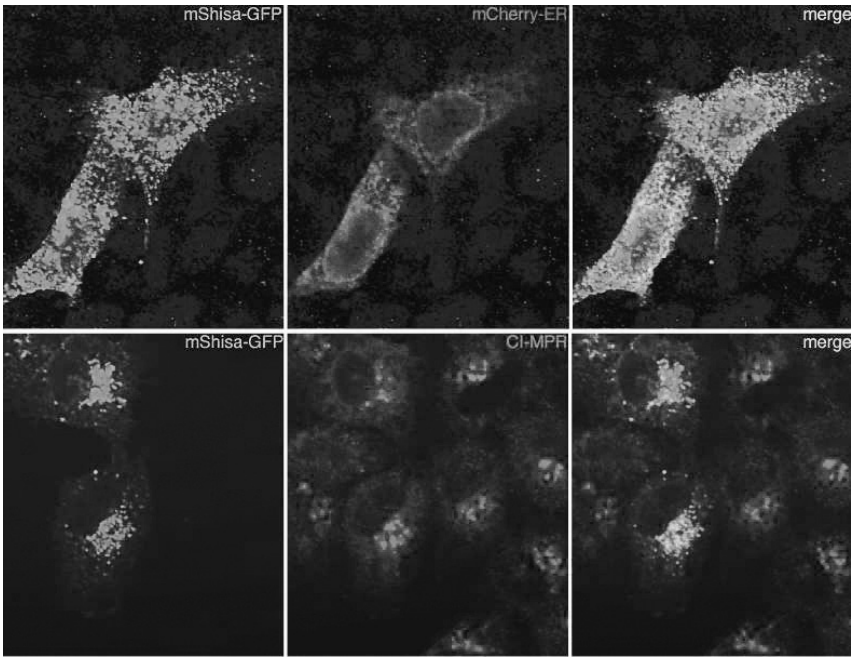

FIGURE 1: The top three images confirm expression of mShisa in the ER.The bottom three images confirm that mShisa is also present in the Golgi complex.

phosphate receptor (CI-M6PR) as a Golgi marker, and, co-localization was identified by confocal microscopy. The top three images of Figure 1 confirm expression of mShisa in the ER. The bottom three images confirm that mShisa is also present in the Golgi complex.

These data demonstrate the presence of Shisa in both the ER and Golgi complex, supporting a potential role for Shisa in the regulation of FGFR2b maturation and therefore its cell surface availability. Alterations in Shisa expression during gut development may be a contributing factor to the development of intestinal atresia phenotypes in which the lack of FGF10/FGFR2b signaling has been implicated.

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Macrophage Targeted Photodynamic Therapy of Inflammatory Atherosclerosis

Neha Jakhete, M.S.II
Research Track
Advisor: Farouc Jaffer, M.D., Ph.D., Assistant Professor of Medicine, Harvard Medical School Cardiology Division, Cardiovascular Research Center, and Center for Molecular Imaging Research, Massachusetts General Hospital, Boston, MA.

Cardiovascular disease complications such as myocardial infarction and stroke are leading causes of death worldwide.[1] Atherosclerosis is an inflammatory vascular disease initiated by lipid deposition into the subendothelial space. Oxidation of retained lipids induces a sustained inflammatory response, recruiting monocytes to the site of injury. Monocytes differentiate into macrophages in an attempt to scavenge oxidized lipids. Unable to regress from the vascular wall, retained macrophages secrete pro-inflammatory and growth factors. Thus, the macrophage is critically involved in atheroma expansion and fibrous cap destabilization. Unstable fibrous caps can rupture, leading to thrombosis and consequent myocardial infarction or stroke.[2, 3] Early identification and treatment of macrophage-rich plaques can significantly limit the morbidity due to atherosclerosis.

Directed therapy of inflamed atherosclerotic lesions is an approach to limit consequences of vascular disease. This study investigated integrated fluorescent imaging and photodynamic therapy (PDT) nanotechnology to ablate inflammatory macrophages, a well-established therapeutic target for atherosclerosis.[4] This strategy aims to stabilize inflamed, macrophage-rich atherosclerotic plaques.[5–7]

PDT involves injectable photosensitizers and subsequent light illumination to induce cytotoxic singlet oxygen formation and apoptosis of diseased cells. Since photosensitizers are light-activated, PDT can be selectively applied, potentially reducing risk of systemic toxicity. Current clinical photosensitizers (i.e. chlorin) lack specific avidity for inflammatory cells within atherosclerotic lesions. To address this issue, our laboratory developed a macrophage-targeted nanoparticle (CLIO, cross-linked iron oxide) conjugated to a photosensitizer that targets plaque macrophages.[5,8,9]

An in vitro assay was developed to assess PDT uptake and efficacy in murine macrophage-type cells (RAW264.7) and compare the efficacy of CLIO-GPC (a new, more chemically efficient photosensitizer) to conventional photosensitizers and control nanoparticles.[10] Two sets of cells were incubated with CLIO-GPC or chlorin at 37°C for 90 minutes. One set of cells then underwent laser illumination for 5 minutes at 100 milli-Watts power while the other set remained in the dark. After 24 hours, cell viability was quantified using the MTS assay to measure magnitude of cell death. The second part of this project repeated the same procedures on primary peritoneal murine macrophages to gauge dosing and potency of the agent before moving to pure in vivo models for testing.

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PHOTODYNAMIC THERAPY

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CLIO-GPC did not induce RAW cell killing as hypothesized. Free chlorin and CLIO-chlorin were more potent inducers of apoptosis (1 percent viability at 20 uM chlorin, 15 percent viability at 5uM chlorin) than GPC or CLIO-GPC. Fluorescent imaging found free GPC to be taken up more readily by RAW cells than GPC conjugated to CLIO, though no cell death was seen upon illumination. However, promising results were seen in primary peritoneal macrophages. While CLIO-GPC did not produce cell death, we did see cell death with free GPC.

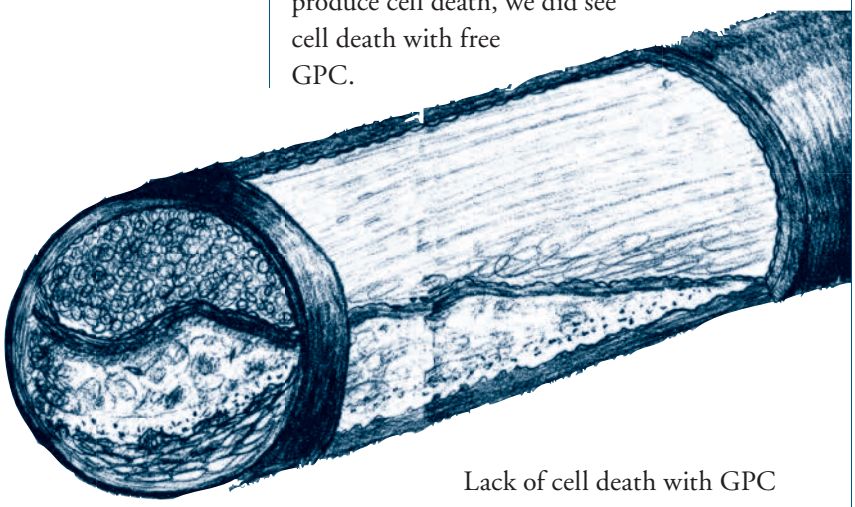

FIGURE 1: Atherosclerosis, by Joan Brumbaugh, M.S.II.

Lack of cell death with GPC could point to a problem with the production of free oxygen radicals when illuminated. More work needs to be done with GPC to understand its potential as a photosensitizer for PDT. Currently its potency is questionable due to reduced cell uptake. However, the CLIO-chlorin results are promising due to both high and targeted cell death. These in vitro results have motivated an in vivo study evaluating the ability of CLIO-chlorin to ablate plaque macrophages in experimental atherosclerosis. These results may have important implications for atherosclerotic treatment via noninvasive (carotid artery) or catheter-based (coronary artery) delivery of excitation light.

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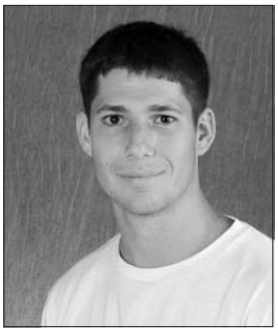
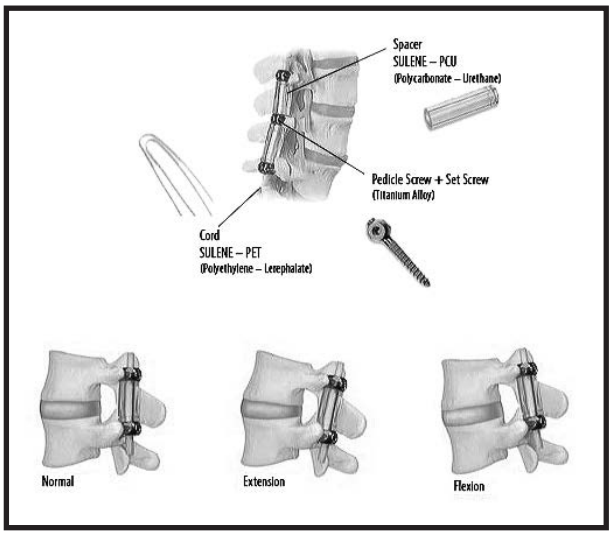
Dynamic Stabilization for the Treatment of Degenerative Spinal Disorders



David Goodwin, M.S.IV
Advisor: Warren Yu, M.D., Associate Professor of Orthopaedic Surgery; Associate Professor of Neurological Surgery Department of Orthopedic Surgery, The George Washington University, Washington, DC.

The field of spine surgery has been revolutionized by advances in technology. Many of these technologies improve existing techniques while others introduce new instruments, procedures, and approaches to degenerative spinal pathology. Historically, spinal fusion has been the gold standard for degenerative spine disease.[1] However, spinal fusion eliminates vertebral motion and places greater mechanical stress on adjacent spinal segments.[2,3] As an alternative, motion-preserving technology, such as the Dynesys Dynamic Stabilization system has emerged. This device is implanted with pedicle screws over the posterior spine, allowing motion at the affected joint location, whereas standard fusion eliminates it. Dynamic stabilization was recently applied at our institution for select patients. This project presents the pre-operative and post-operative outcomes of this device.



In this study, we reviewed charts for consecutive patients who received the Dynesys Dynamic Stabilization system for the treatment of degenerative spinal disorders. This retrospective review followed 17 patients for an average of 5.3 months. Questionnaires completed pre-operatively and at each post-operative follow-up clinical exam assessed the patients' quality of life and current pain levels.

Based on the Oswestry Low Back Pain and Disability Scale, patients receiving Dynesys Posterior Dynamic Stabilization had a 48 percent reduction in pain levels from their pre-operative state. To measure specific regions of pain, we used the Visual Analog Scale. Based on this measure, patients reported a 42 percent improvement in leg pain and a 55 percent improvement in back pain.

The Dynesys Dynamic Stabilization technology presents a new approach to treating degenerative spinal disorders. It has several biomechanical advantages over fusion and has demonstrated clinical success in this cohort of patients.

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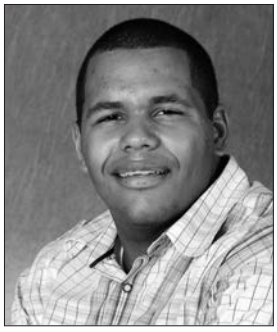

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Incidence and Risk Factors of DVT and PE following Major Spinal Surgery

Orthopaedic surgery carries a significant risk for developing deep vein thrombi (DVT) and pulmonary emboli (PE) due to the associated bleeding and clotting. [1] Without prophylaxis, 43 percent of post surgical spine patients will develop DVT.[2] Pre-spinal surgery chemical anticoagulation is contraindicated as it has resulted in 0.2 percent incidence of epidural hematoma significant enough to require another operation.[3,4] Pneumatic compression stockings reduce the combined DVT plus PE incidence to 0.29 percent – 3.5 percent.[2,5] The Transforaminal/ Posteriorforaminal Lumbar Intrabody Fusion (TLIF/PLIF) surgical procedure has been shown to be a risk factor for the development of DVT and PE.[6] Our hypothesis is that the incidence of DVT and PE is a function of patient risk factors and co-morbidities and not of the type of surgical procedure performed (e.g. TLIF/PLIF).[7] Therefore, the purpose of this study is to provide a large scale analysis of DVT and PE surgical procedure risk, co-morbidities, and incidence.

This project determined the incidence and risk factors of DVT and PE following major spinal surgery performed by two surgeons in the Department of Orthopaedic Surgery at The George Washington University Hospital.

Data were obtained by retrospective chart review of 1,502 surgeries performed from 2001–09. Datapoints recorded included procedure type, body mass index (BMI), smoking history, age, medical co-morbidities, DVT prophylaxis employed, length of stay, and any DVT risk factors. For the purpose of this review, DVT risk factors were classified as previous DVT/PE, previous or active malignancy, the use of estrogen replacement therapy (ERT), and the use of oral contraception. We found that the incidence of DVT plus PE of 1.1 percent (Table 1) was lower than that reported by Epstein of 3.5 percent, but higher than that recorded by Nicol of 0.29 percent.[2,5]

The following significant risk factors for DVT and PE are displayed in Graph 1: active malignancy, previous DVT/PE, ERT, discharge to home versus rehab, major depressive disorder (MDD), hypertension (HTN), renal disease, congestive heart failure (CHF), and benign prostatic hypertrophy (BPH).

Analysis showed that the following were not significant risk factors: smoking, multiple procedures within 30 days, obesity, gender, GERD, hyperlipidemia, and sleep apnea. Contrary to Nguyen and colleagues, relative risk calculations for TLIF/PLIF surgery show no increased risk for DVT plus PE ($p = 0.8$).[6]

As a result, the study hypothesis is not rejected, as TLIF/PLIF surgical procedures are not shown to be a significant risk factor and several patient risk factors and co-morbidities were shown to be significant. The cause of the difference in DVT plus PE incidence between Epstein, Nicol, and this study is unknown.[2,5] This study identified new risk factors: MDD, HTN, BPH. Increasing prophylaxis measures for patients with these co-morbidities may be indicated. Future studies are encouraged to look at the level of prophylaxis used on patients versus DVT and PE incidence. Specifically, the relationship of DVT plus PE incidence versus how many hours postoperatively chemical anticoagulation is administered should be

TABLE 1: INCIDENCE OF DVT AND PE FOLLOWING MAJOR SPINAL SURGERY.

Number of surgeries analyzed for DVT/PE's	1502
Number of DVT counted	6
Number of PE counted	11
Number of DVT+PE	17
Incidence of DVT	0.4 percent
Incidence of PE	0.7 percent
Incidence of combined DVT + PE	1.1 percent

explored. In addition, future prospective studies might look at management of co-morbidities.

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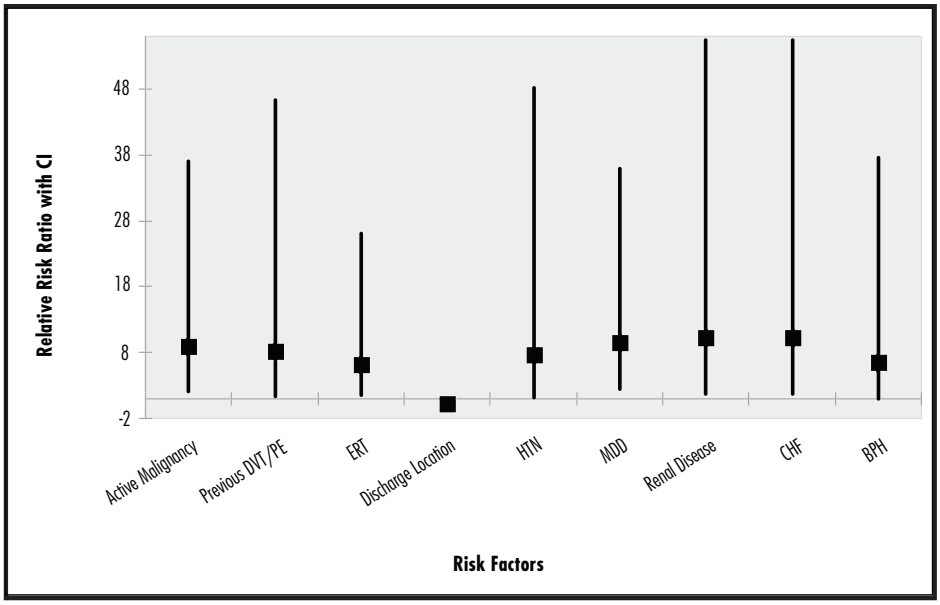

GRAPH 1: Significant DVT/PE Risk factors after spinal surgery. Factors that increase risk are active malignancy, previous DVT/PE, ERT, HTN, MDD, renal disease, CHF, and BPH. Discharging the patient to home, versus rehab, decreases risk.

Outcomes of Patellar Realignment for Patellofemoral Arthritis in Young Patients

One of the most common symptoms of people seeking treatment from orthopedic surgeons is anterior knee pain associated with patellofemoral arthritis.[1] Conservative methods to alleviate symptoms of patellofemoral arthritis, including physical therapy, bracing, or hyaluronic acid injections, can help relieve some of the mechanical symptoms, pain, and swelling, but relief is often temporary.[1–5] If conservative methods fail, there are a variety of surgical interventions for treatment of patellar pain and instability, but few target patellofemoral arthritis specifically.[1–4] Selecting the best operative method depends on patient age, activity level, the severity and the location of the chondral damage.[2,3]

Patellar realignment consisting of tibial turbercle osteotomy with anterior and medial transfer of the tibial tubercle (Figure 1) was originally described in 1983 by J.P. Fulkerson et al.[7,8] Transferring the tibial tubercle anteriorly and medially aims to maintain the extensor mechanism and shift the load off of the painful, degenerated area of cartilage.[3–7] Previous studies using tibial tubercle anteromedialization procedures have described good results for the treatment of patellar instability and, more recently, for the treatment of patellofemoral arthritis in the adult population above 50 years old.[1,3,4,6,8–10]

However, the success of patellar realignment for the treatment of patellofemoral arthritis remains largely unknown, especially in the younger population where maintaining functional ability is of primary importance.[9] The objective of this study was to determine the effectiveness of patellar realignment through tibial tubercle anteromedialization in treating

PATELLAR REALIGNMENT *Continued on p. 14*

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localized patellofemoral arthritis in patients under of 42 years of age.

Between October 2003 and October 2007, the tibial tubercle anteromedialization procedure was performed on 24 knees (18 patients) by a single surgeon (R.V.W.) for the treatment of localized patellofemoral arthritis. Results were retrospectively reviewed at a mean 3.6 years after surgery. Correlations between age, length of follow-up, degree of chondral damage, and mean BMI were made with the IKDC Subjective Knee Evaluation Form score evaluated at follow-up. Patients' charts and preoperative radiographs were reviewed in order to correlate physical exam and pre-operative radiographic measurements with the final results (Figure 2). Outcomes were determined using standard physical examination modalities, the IKDC Subjective Knee Evaluation Form, and patient-directed questions regarding satisfaction with the surgery.

FIGURE 1. Postoperative AP and lateral radiographs demonstrating the position of the patella, tubercle, and hardware.

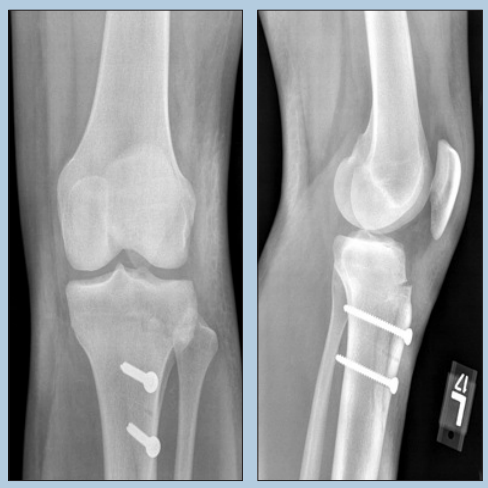
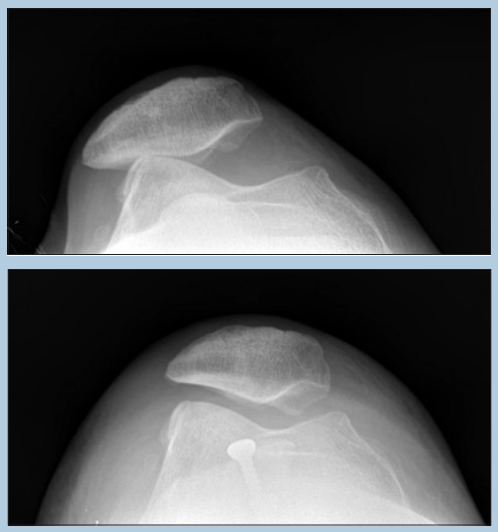


FIGURE 2. Preoperative and postoperative Merchant radiographs demonstrating realignment of the patella.



Patellar realignment was performed on 24 knees (18 patients). There were fourteen women and four men with a mean age of 27.8 years and a BMI of 29.6. The mean IKDC score was 72.8 at an average length of follow-up of 3.6 years. The IKDC score was not significantly associated with age, length of follow-up, BMI, congruence angle, patellar height, or grade of chondrosis. All but two patients (three knees) reported to be greatly or somewhat improved by the surgery and all but two patients (two knees) would undergo the surgery again.

This data suggests that patellar realignment can be performed in properly selected young patients with localized patellofemoral arthritis and can result in good outcomes. Although patient IKDC scores do not meet the normative IKDC scores for the age and gender matched population, the majority of patients felt that their condition was greatly improved with the surgery and would opt to have the surgery again. Patellar realignment through tibial tubercle anteromedialization should be considered as a good option in treating patellofemoral arthritis in the young population when conservative treatments have failed to provide relief from pain.

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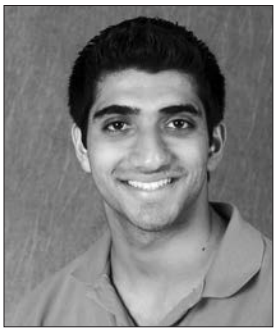
Volumetric Analysis Reveals White Matter Volume Loss in Adults with Partial Ornithine Transcarbamylase Deficiency (OTCD)



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The urea-cycle disorders (UCDs) are a rare group of inborn errors of metabolism that result in failure to convert ammonia to urea, leading to hyperammonemia and substantial cognitive and motor deficits. Ornithine Transcarbamylase Deficiency (OTCD) is the most common UCD, with symptoms of protein intolerance and deficits in executive functioning, working memory, and motor planning. As ammonia crosses the blood-brain barrier, it becomes trapped in the brain. In order to buffer excess ammonia, astrocytes combine glutamate with ammonia to form glutamine via the enzyme glutamine synthetase. Glutamine is not as toxic as ammonia, but is osmotically active in astrocytes; excess glutamine results in astrocyte swelling, which can lead to cerebral edema, increased intracranial pressure, or coma. This mechanism is thought to explain the white matter damage associated with hyperammonemia,but there have been no quantitative measures of white matter volume in this disorder.[1]

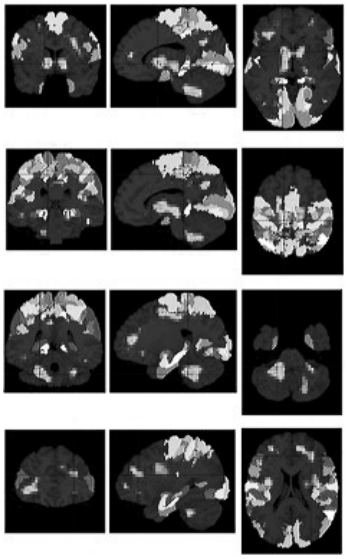

FIGURE 1:
Cross hair marks WM loss of internal capsule.

Cross hair marks WM loss of superior corona radiata.

Cross hair marks WM loss of cerebellum.

WM loss of diffuse areas of frontal cortex.

The purpose of this study was to quantitate white matter volume (WMV) in OTCD patients by using a voxel-based morphometry (VBM) approach. VBM is a neuroimaging analysis technique that allows comparison of the local concentration of matter between groups of subjects, and it involves normalizing the images into the same stereotactic space.[2] The hypothesis was that decreased WMV would be observed.

High-resolution 3D MRI data were acquired from 22 adult patients with partial OTCD and 22 healthy age-matched volunteers without neurological impairment (Figure 1). The subject group included late onset males with OTCD as well as both asymptomatic and symptomatic females heterozygous for OTCD, with varying ages of diagnosis and metabolic control. VBM was performed on a PC using Matlab 7.4 and SPM5 software.

VBM analysis showed that OTCD patients have less white matter volume than age matched controls ($p < 0.0385$ False Discovery Rate). Depicted are the results of a two-way-t-test showing differences in white matter volumes. The colors indicate areas of decreased volume on an intensity scale.

There was damage to the anterior limb of the internal capsule and the superior corona radiata. These two connected white matter sheets are important for communication between the cortex and subcortical structures; information flows from the thalamus through the internal capsule and corona radiata until it reaches the cortex. The corona radiata coalesces on to the centrum semiovale, the white matter core of the cerebral hemispheres that has been shown to be damaged in previous studies on OTCD.[3] There was also white matter loss in the cerebellum ($p < 0.0385$), an area known for its role in coordination and motor control. This could explain the common symptom of decreased fine motor control found in typical OTCD patients. There was diffuse white matter loss in the frontal cortex, the area of the brain responsible for executive function, which could explain the cognitive deficits seen in OTCD patients.

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Variables Associated with the Acceptance of Acupuncture among Children with Cancer: Interim Analysis of a Prospective Study

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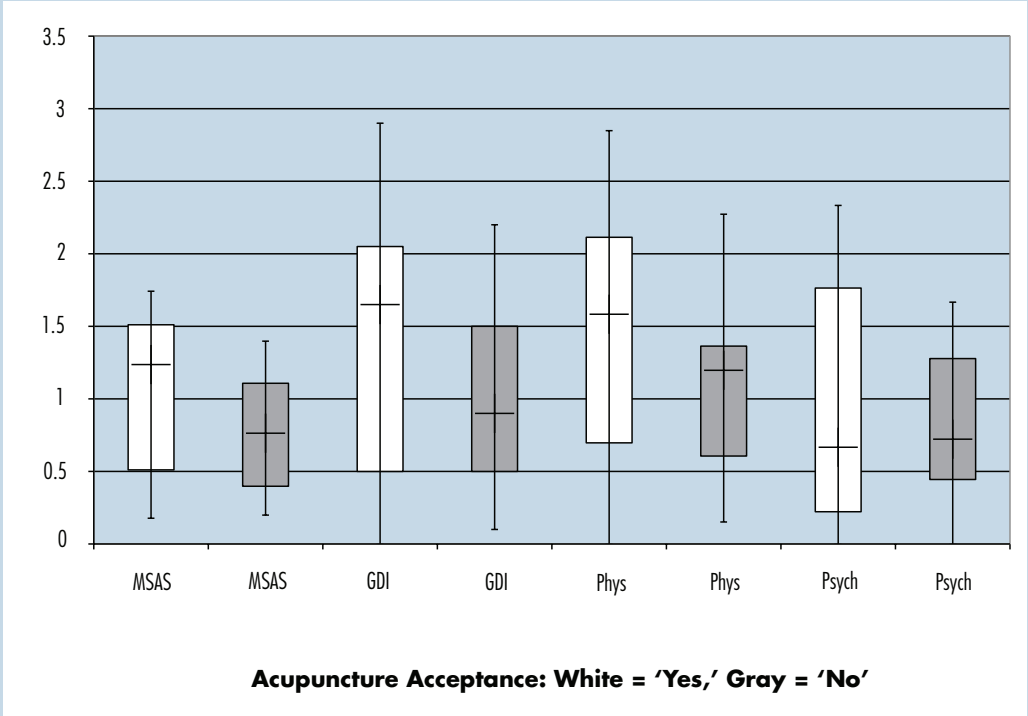
The safety and feasibility of acupuncture as supportive care treatment for children with cancer has been reported previously, yet the reasons for using acupuncture have not been a specific focus of research.[1–3] In this prospective study, variables associated with acceptance of acupuncture are investigated.

This study is currently ongoing at the Integrative Therapies Program for Children with Cancer at Columbia University Medical Center. All acupuncture-naive patients were eligible for inclusion. Upon enrollment, patients or parent/guardian completed the Memorial Symptom Assessment Scale (MSAS) every three weeks for six months.[4] Patients were offered treatment with acupuncture or other integrative services each time the MSAS was completed. If acupuncture was accepted, a pre- and post-acupuncture questionnaire was administered which included information on reasons, expectations, and satisfaction with acupuncture. MSAS scores, physical symptom subscores, psychological symptom subscores, and global distress indices were calculated for each patient over the six months.

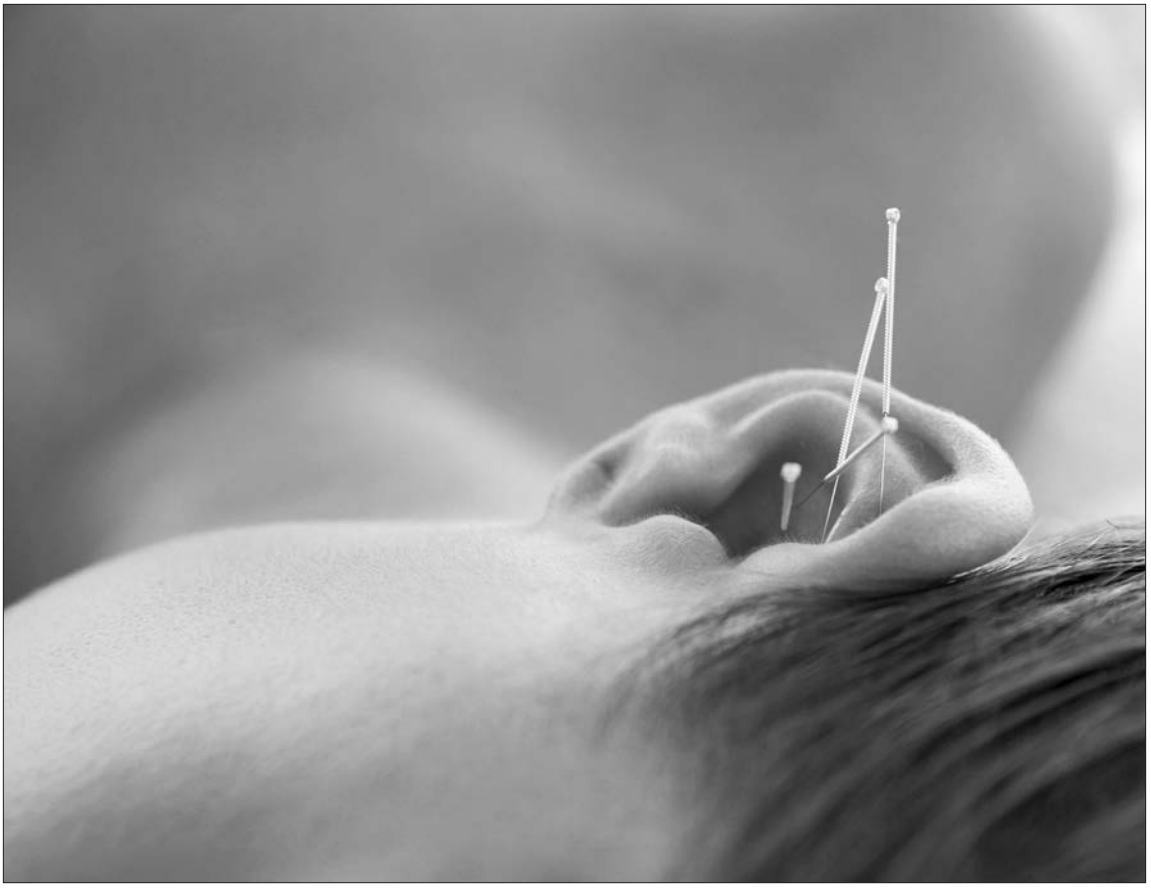
Twenty-five patients (12M/13F) were recruited. Patient diagnoses were leukemia/lymphoma (15), brain tumor (4) and solid tumor (6). Eight patients accepted acupuncture over the six-month period (3M/5F; 32 percent). Thirty-one acupuncture and 192 non-acupuncture treatments were administered. The median number of days to acceptance of acupuncture was 16 (Range 0–159). The median number of acupuncture treatments per patient was 2.5 (Range 1–11). Acupuncture acceptors were older than non-acceptors (median 15.5 years vs. eight years, p=0.0005). The most prevalent symptoms (>80 percent) in acupuncture acceptors were cough, difficulty sleeping, pain, nausea, headache, changes in taste, constipation, and numbness/tingling. The most prevalent

FIGURE 1: Maximum MSAS Subscale Scores by Acupuncture Acceptance



* For each subscore, the maximum score prior to acupuncture acceptance or maximum score over the total six months for non-acceptors was used.

FIGURE 1: Although all patients experienced similar therapy-related symptoms, children who accepted accupuncture had hgher scores on the Memorial Symptom Assessment Scale, including the Global Distress Index, and Physical Symptom subscales.



symptoms (>80 percent) in non-acceptors were pain, cough, nausea, hair loss, feelings of being irritable, lack of appetite, vomiting, difficulty sleeping, and lack of energy. Children who accepted acupuncture reported slightly more symptoms over the six-month period compared to children who did not (Medianacu =11.7 vs. Mediannon-acu =8.6). When examining maximum MSAS scores, which take into account the frequency, severity, and distress of symptoms, we found that patients who accepted acupuncture had higher MSAS scores, physical symptom subscores, and global distress indices compared to non-acceptors (Figure 1). These differences were not statistically significant. However, similar trends for each subscale were seen when we analyzed the average MSAS scores over the entire study period.

Age is an important factor in acceptance of acupuncture. Children who receive acupuncture seem to report a similar constellation of symptoms as children who do not receive acupuncture. However, children who accept acupuncture may experience these symptoms at a greater frequency, increased severity, or at heightened distress. Subsequent analyses with the entire study population will be necessary to validate these initial findings. Evaluation of variables related to the acceptance of acupuncture, including therapy-associated side effects and symptoms, may identify those patients likely to benefit most from acupuncture services.

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Disruption of Functional Anatomy in Listening and Reading Comprehension Tasks in Childhood Epilepsy

Epilepsy populations often have greater atypical language representation and often have (subtle) impairments in language functions; thus we aimed to look at connectivity beyond language dominance. The actions of listening to and reading stories show strong activation along the superior temporal sulcus, and consistent left laterality across ages in the inferior frontal gyrus, middle frontal gyrus, and posterior temporal regions. Cortical functional connectivity, as indicated by the concurrent spontaneous activity of spatially segregated regions, may determine the reaction of the brain to external stimuli and task requirements and appears altered in many neurological and psychiatric disorders.[2] Just et al. (2004) found consistently lower functional connectivity grouping autism when compared to controls. This group's findings suggest that autism affects information integration and neural processing.[3]

There were 59 healthy controls (4–12 year-olds) and 43 left focus localization-related epilepsy patients (4–12 year-olds) evaluated using two fMRI language tasks (reading comprehension and listening comprehension) obtained at 3T with EPI BOLD techniques. fMRI maps were interpreted at a standard threshold and laterality and connectivity data was gathered using spm2. Healthy controls with frontal activation have higher laterality in the middle frontal gyrus (MFG) and inferior frontal gyrus (IFG) (p=.022, p=.062) for the listening task. These controls also have lower connectivity values in IFGR-IFGL and MFGR-MFGL than patients without frontal activation (p=.027, p=.062). When comparing LI values between patients and healthy controls, there are no differences in their laterality of language in IFG and WA but there is a trend for MFG variance between groups (patients n=43, healthy controls n=59, p=.10). Patients for the

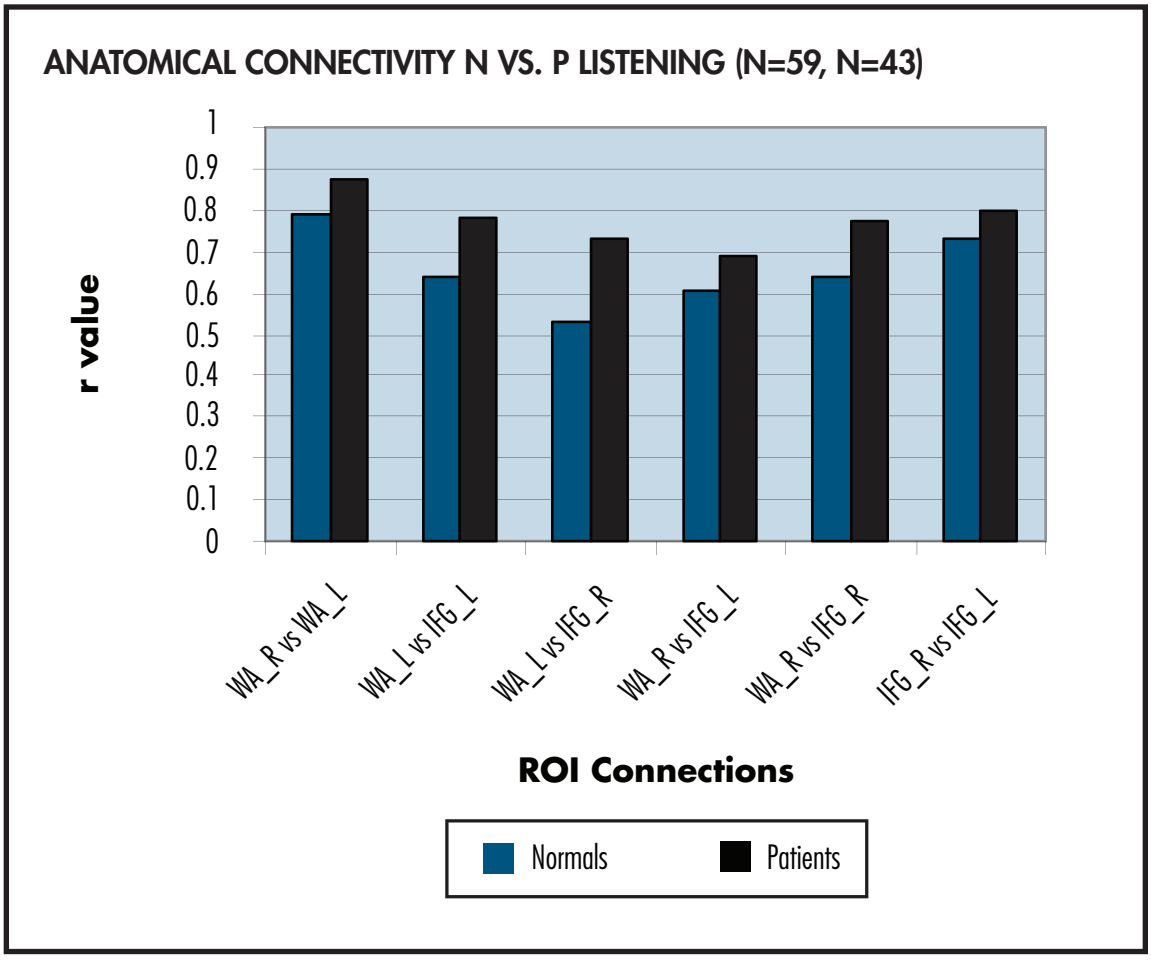

FIGURE 1: Relationship of group to connectivity (Pearson's r-value).

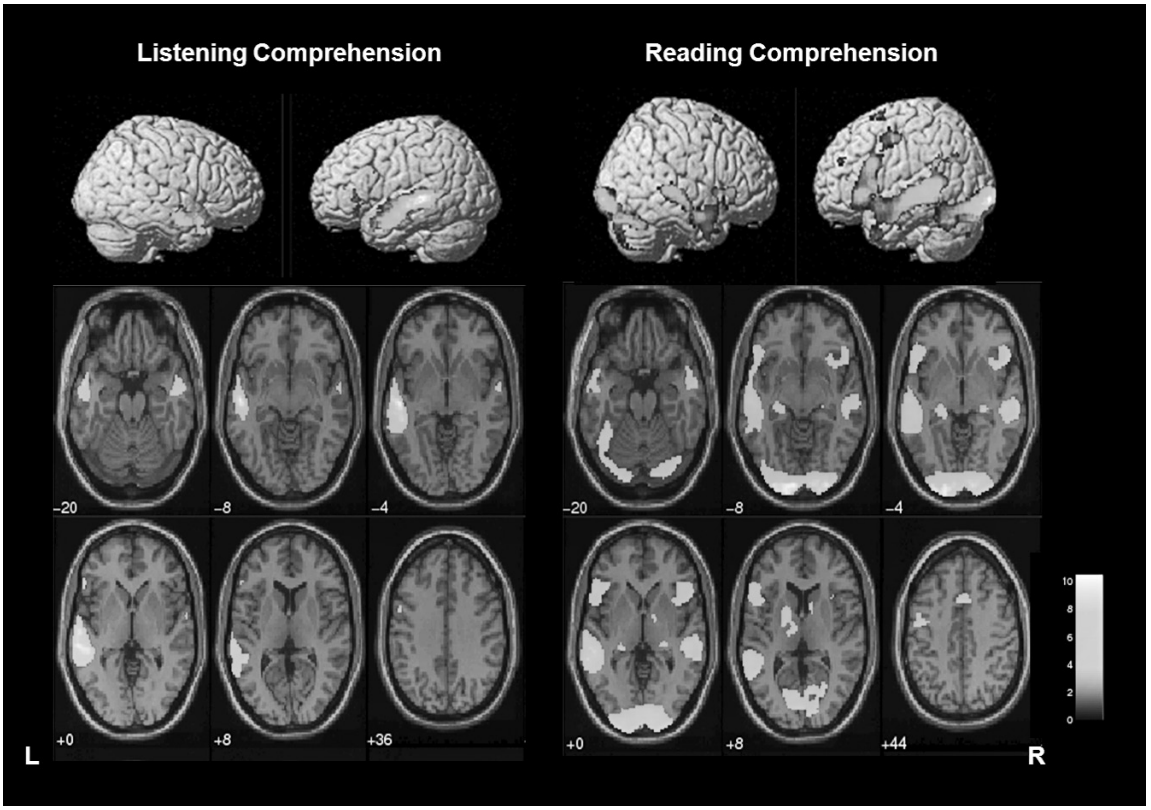

FIGURE 2: Group Activation Maps for our healthy control group.

listening task show stronger connectivity values than healthy controls in IFGR-IFGL, WAL-IFGL, MFGR-MFGL, and WAR-WAL ($p<.01$) (Figure 1). In our patient population and healthy control group, connectivity values did not vary by age.

Patients for the reading task have more atypical language representation in MFG and WA than healthy controls ($p=.015$, $p=.016$) and overall more atypical language representation in all areas ($p=.021$). There were no connectivity differences between healthy subjects and patients in IFGR-IFGL, WAL-IFGL, and MFGR-MFGL; for WAR-WAL, there are stronger connectivity values in patients than in controls ($p<.001$).

Our reading comprehension task was targeted to identify dominant middle temporal gyrus and superior temporal gyrus in addition to dominant IFG and MFG. Our listening task was targeted to identify temporal receptive cortex regions along the dominant superior temporal sulcus.[4] Further progression of this project will include group activation maps created from our patients while they performed these tasks to see if they have activation patterns consistent with these studies' findings; a comparison between these group maps and the healthy control group maps (Figure 2) would be of interest in establishing whether or not left-focus epilepsy affects the strength of activation in these areas. Our research has found that connectivity is similar between patients and controls, with some modest differences that may relate to working memory issues. Our next step is to look at connectivity differences between patients with typical and atypical language representation.

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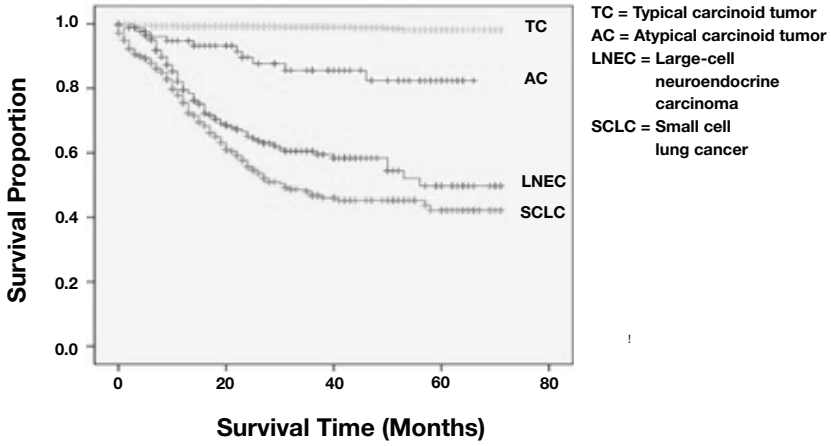
Resected Pulmonary Atypical Carcinoid and Other Bronchopulmonary Neuroendocrine Tumors: A Comparison of Clinical Presentation and Survival

Pulmonary atypical carcinoid (AC) and typical carcinoid (TC) tumors are in the bronchopulmonary neuroendocrine tumor (BPNET) classification that includes large-cell neuroendocrine carcinoma (LCNEC), and small cell lung cancer (SCLC).[1] Previous small scale studies suggest that resected pulmonary AC has a clinical presentation and survival pattern distinct from TC. We reviewed a large epidemiologic cancer database, and hypothesized: 1) resected pulmonary TC will show a favorable clinical presentation and survival pattern, 2) resected AC will show a clinical presentation and survival pattern similar to LCNEC and 3) resected SCLC will demonstrate the least favorable clinical presentation and survival pattern.

The Surveillance Epidemiology and End Result database was queried to compare demographic (age, gender, ethnicity) and tumor specific clinical variables (including nodal status and stage) in 2239 patients diagnosed with, and undergoing lobectomy for TC, 145 patents with AC, 510 patients with LCNEC and 1521 patients with SCLC from 2001 to 2006. We performed univariate analysis of clinical variables and analysis of survival among the BPNET histologic types.

AC patients presented at a similar age of diagnosis (Mean 59.9 years) as TC patients (Mean age 58.5) but younger than LCNE and SCLC patients (Mean age of 65.3 and 66.2 respectively, $P < 0.001$). AC and TC had higher predilection towards female patients (70.3 percent and 68.7 percent) than LCNE and SCLC (45.7 percent and 51.4 percent, $p < 0.001$). All BPNET patients had a statistically equal predilection to white ethnicity. AC patients had greater incidence of histologically positive lymph nodes and higher pathologic stage compared to TC, similar to LNEC but more favorable than SCLC ($p < 0.001$). Survival analysis showed a step wise mean survival of 40.0 ± 1.9 months for SCLC, 46.2 ± 2.2 months for LCNEC, 58.3 ± 2.5 months for AC tumors, and 70.2 ± 0.2 months for TC tumors. TC patients demonstrated favorable survival and SCLC patients poorer survival compared to AC and LNEC patients (Figure 1).

FIGURE 1



TC and SCLC tumors are histologies that exhibit clinical behavior distinct from AC and LCNEC. Atypical carcinoid tumors should be staged and treated with stage appropriate neoadjuvant and adjuvant therapeutic strategies similar to LCNE and other non-small cell lung cancers.

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Identification of Aspirin Resistant Biomarkers Using Whole Blood Genome Profiling

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Cardiovascular disease (CVD) is the leading cause of death in the industrial world, where one in three adults are diagnosed with CVD.[1] Acute coronary syndromes alone account for 30 percent of all deaths in the U.S. each year.[2] Atherosclerotic plaque formation and rupture accounts for the majority of acute coronary syndromes, as these trigger platelet aggregation leading to arterial occlusion. The most commonly prescribed inhibitor of platelet aggregation is acetylsalicylic acid, commonly known as aspirin. The effectiveness of aspirin has been questioned in past years. Clinical studies revealed that as many as 20 percent of patients taking aspirin have recurrent ischemic vascular events, suggesting that aspirin may be ineffective for some people. These clinical findings inspired the term aspirin resistance (AR). The underlying causes of AR are unknown, and few clinical studies attempt to describe them. Some attribute AR to an inadequate dosage of aspirin, patient non-compliance, difference in absorption, or genetic causes.[3] Our research study attempts to identify possible biomarkers, which could be used to diagnose patients as AR via genetic profiling.

Aspirin resistance is measured using the Verifynow® System. Patients with 550 Aspirin Reaction Units (ARU) or more are considered AR, while patients below 550 ARU are considered aspirin-sensitive. Gene expression profiling was conducted on eight aspirin-sensitive (424 ARU ± 37 σ) and eight resistant patients (568 ARU ± 15.4 σ) via the Affymetrix HG-U133 2.0 GeneChip arrays. Using GeneSpring 10.0, genes satisfying two parameters, P-value (≤ 0.05) and fold change (FC ≥1.8, 2.0), were calculated and then considered for further analysis and assays using Pathway Studio 6.1 and Ingenuity Pathway Analysis (IPA).

The gene expression profile indicated that 284 genes ($p \leq 0.05$, FC ≥ 1.8) were differentially expressed, of which 61 genes were strongly differentially expressed (FC ≥ 2.0). Notably, pathway analysis (Figure 1) revealed that prostaglandin E synthase (PGES, FC= +3.62) and thrombospondin-1 (THBS1, FC = -2.17) are closely related to cell adhesion.

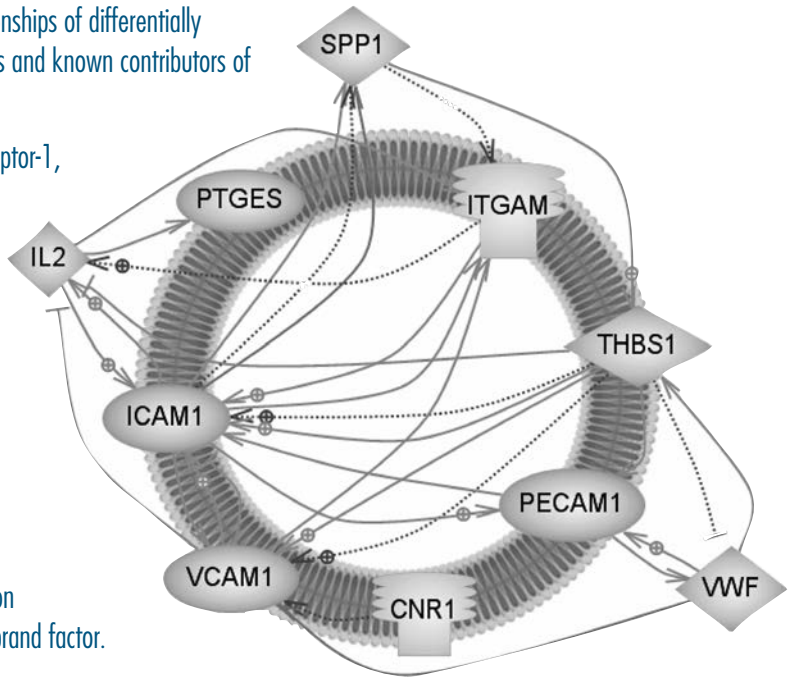
In search of potential biomarkers for AR, gene expression profiling of AR patients revealed that PGES is significantly upregulated. PGES synthesizes PGE2, a metabolite downstream of COX that causes both pro- and anti-coagulation effects downstream upon release from activated platelets as a function of its concentration. Membrane-bound PGES synthesizes PGE2 from [PG]H2 derived from COX-1 and a related enzyme, COX-2.4 The COX-2/PGES pathway is resistant to aspirin and could represent an alternative route to blood coagulation.

ASPIRIN

Continued on p. 22

FIGURE 1: Functional relationships of differentially expressed genes in AR patients and known contributors of cell adhesion.

CNR1 = Cannabinoid Receptor-1, ICAM1 = Intercellular Adhesion Molecule-1, ITGAM = Integrin Alpha-M, PECAM1 = Platelet/endothelial cell adhesion molecule 1, PTGES = prostaglandin E synthase, SPP1 = secreted phosphoprotein-1, THBS1 = thrombospondin-1, VCAM1 = vascular cell adhesion molecule-1, VWF = von Willebrand factor.



ASPIRIN

Continued from p. 21

Another potential biomarker of interest is THBS1 due to its close functional relationship with von Willibrand Factor (vWF). vWF is a multimeric protein that promotes adhesion of platelets to sites of vascular injury. THBS1 inhibits blood coagulation by decreasing vWF multimer size.[5] Our gene expression profile indicates that THBS1 is significantly down-regulated, which suggests that vWF has a higher hemostatic competence in AR patients.

Patients resistant to aspirin remain unknowingly at risk for sudden cardiovascular events. Our gene expression profiling identified several promising pathways that could explain the aspirin resistance phenotype. Further investigation will be required to determine the contribution of these pathways to aspirin resistance.

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Association of Atrogin-1 Genotypes with Baseline Muscle Phenotypes in Men and Women

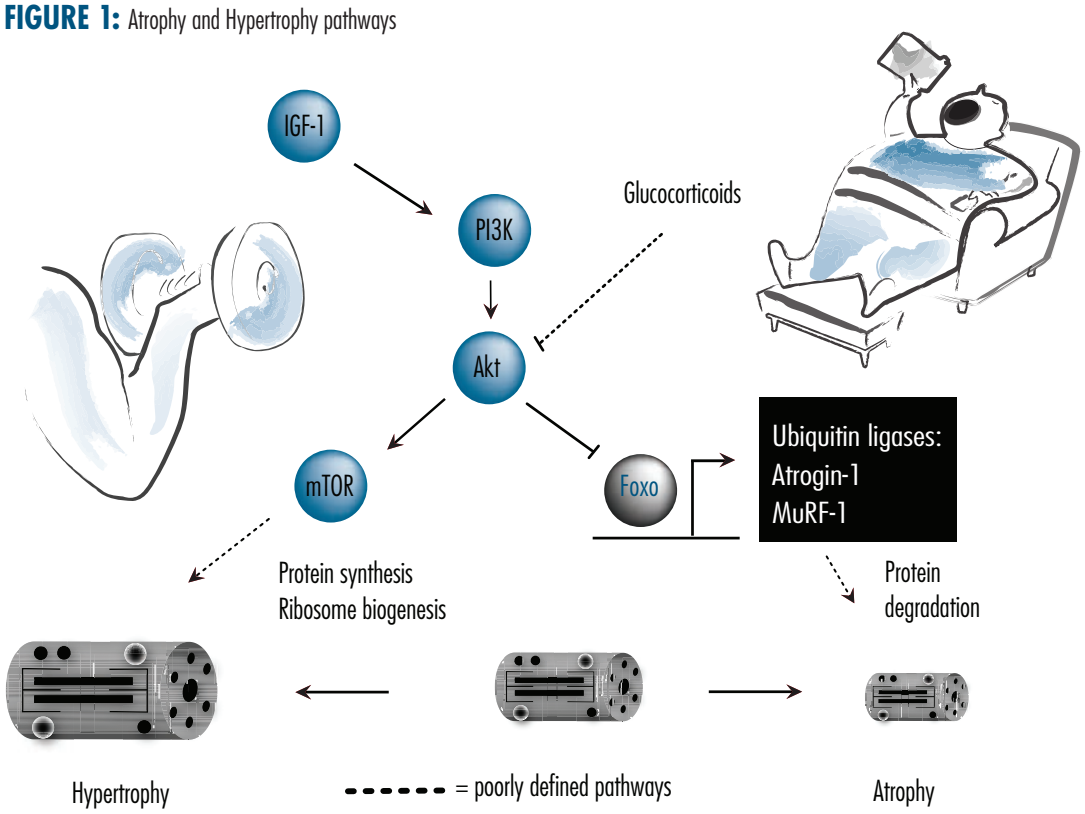
The maintenance of muscle mass is regulated by a balance between protein synthesis and protein degradation pathways; a balance shifted toward protein degradation during atrophy. Muscle atrophy occurs as a consequence of various conditions, such as aging, bed rest, cancer, denervation, injury, and joint immobilization. The increased proteolysis in atrophying muscles results from the activation of the ATP-dependent ubiquitin proteasome proteolysis pathway.

Atrogin-1 is an ubiquitin-protein ligase (E3) that is a critical component of the ubiquitin-proteasome pathway (Figure 1), expressed specifically in striated (cardiac and skeletal) muscle. It directs the breakdown of muscle protein in response to various conditions (ex. disuse, cancer, starvation), and it is down-regulated during the hypertrophy response. As a result, Atrogin-1 has strong potential as a modifier of muscle size and strength. Examining genetic variation in the Atrogin-1 gene may help explain inter-individual differences in muscle size and strength, as well as differences in the response to resistance training.

Seven hundred fifty-eight Caucasian college-aged subjects (446 females; 312 males; age 24 ± 8 y) participated in a 12 week supervised strength training program for the upper arm muscles (biceps and triceps). The program consisted of two 45–60 minute sessions per week for 12 weeks, as each session was supervised by an exercise physiologist professional or a trained student. Muscle size (via MRI) and strength measurements (1 RM and isometric) were taken before and after training. The study participants were then genotyped for five Atrogin-1 Single Nucleotide Polymorphisms (SNPs); rs4871385, rs6990663, rs3739287, rs2891779, and rs16898553. A list of the SNPs that were genotyped and their positions in the Atrogin-1 gene can be found in Table 1. Genotyping for the Atrogin-1 SNPs was performed using the TaqMan allele discrimination assay. Associations between the SNP and each phenotype were tested using ANCOVA with Sidak post-hoc tests.

Significant associations between Atrogin-1 SNPs and several muscle phenotypes were found. The most significant results were found in females with the rs2891779 SNP, which is located in the promoter region of the Atrogin-1 gene. Specifically, when a dominant model was applied, females having one or two copies of the A allele had significantly higher baseline isometric strength, torque, and muscle quality

FIGURE 1: Atrophy and Hypertrophy pathways



Based on Hoffman EP, Nader GA. *Nat Med.* 2004;10(6):584–5.

than those who were homozygous for the G allele. These same associations were seen in both the dominant and non-dominant arms.

This data suggests that the Atrogin-1 rs2891779 SNP influences baseline muscle strength, torque, and muscle quality in females, which may indicate a sex-specific effect for this SNP. The location of this SNP in the promoter region of Atrogin-1 suggests that it may exert its influence through regulation of Atrogin-1 expression. This data contributes additional insight to the complex genetic milieu that affects muscle size and strength.

Gene	GeneID	Rs#	RefSeq	Position on MRNA
Atrogin-1	114907	rs4871385	NM_05229.2	225 (Synonymous cds)
Atrogin-1	114907	rs6990663	NM_058229.2	-11,757 upstream of mRNA
Atrogin-1	114907	rs3739287	NM_058229.2	798 (Synonymous cds)
Atrogin-1	114907	rs2891779	NM_058229.2	-2,387 upstream of mRNA
Atrogin-1	114907	rs16898553	NM_058229.2	-2,560 upstream of mRNA

TABLE 1: Single Nucleotide Polymorphisms and their positions in Atrogin-1.

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AKT2 Gene Variants Are Associated with Muscle Phenotypes in Both Men and Women

The purpose of this study was to examine whether AKT2 Single Nucleotide Polymorphisms (SNPs), were associated with muscle strength and size phenotypes and responsiveness to resistance training in men and women. The gene variants tested were: rs2304186 (3' UTR regulatory region), rs969531 (5' UTR regulatory region), and rs892118 (intronic region).

The AKT serine/threonine kinase is involved in various important cellular events such as cell survival, proliferation and differentiation, as well as insulin-stimulated glucose metabolism and cellular protein synthesis.[1,2] Activation of AKT is essential for cell survival during myogenesis, and consequently AKT activity increases during myogenesis.[3] Several studies have demonstrated that expression of the AKT2 isoform in particular is significantly elevated during skeletal muscle differentiation.[2,4,5,6] Since AKT2 is activated by exercise and muscle contraction in both rodents and humans, it is an attractive target gene for studying human skeletal muscle size and function pre- and post-resistance training.[7]

In this prospective genome-wide association study, 753 Caucasian subjects (449 female, 304 male) [from the FAMUSS cohort] were enrolled in a resistance-training program. The phenotypes being measured included muscle strength and muscle and fat volume. All phenotype measures were examined before and after a 12-week training program. For each SNP, a Chi-square analysis was used to test Hardy-Weinberg equilibrium. Associations between each SNP and phenotype measure were tested with Sidak post-hoc tests. Each model included baseline body weight and age as covariates and used a dominant genetic model.

We found that the AKT2 rs2304186 variant was significantly associated with baseline subcutaneous fat in males only (Table 2). Males with a copy of the T allele demonstrated a significantly

AKT2 VARIANTS *Continued on p. 25*

TABLE 1. ANALYSIS OF AKT2 SNPS WITH 1-RM STRENGTH, ISOMETRIC STRENGTH AND WHOLE MUSCLE VOLUME IN FMS CAUCASIANS:

Phenotype	Gender	AKT2 (rs7254617)	AKT2 (rs892118)	AKT2 (rs2304186)	AKT2 (rs969531)
Baseline 1-RM strength	Female	1.02; NS	1.62; NS	0.46; NS	0.07; NS
Difference in 1-RM strength	Female	2.18; NS	1.66; NS	0.42; NS	0.43; NS
% change in 1-RM strength	Female	2.11; NS	2.38; NS	1.16; NS	1.01; NS
Baseline isometric strength	Female	0.45; NS	1.23; NS	0.27; NS	0.16; NS
Difference in isometric strength	Female	0.11; NS	0.51; NS	0.36; NS	**5.33; 0.0051**
% change in isometric strength	Female	0.22; NS	0.52; NS	0.13; NS	3.95; 0.0198
Baseline whole muscle volume	Female	1.32; NS	0.61; NS	0.54; NS	0.69; NS
Difference in whole muscle volume	Female	0.31; NS	0.21; NS	0.20; NS	0.24; NS
Baseline 1-RM strength	Male	0.24; NS	0.09; NS	**5.17; 0.0062**	0.28; NS
Difference in 1-RM strength	Male	0.11; NS	0.12; NS	4.20; 0.0160	0.46; NS
% change in 1-RM strength	Male	0.36; NS	0.52; NS	**6.87; 0.0012**	0.14; NS
Baseline isometric strength	Male	0.28; NS	0.07; NS	0.10; NS	0.52; NS
Difference in isometric strength	Male	0.48; NS	0.15; NS	3.38; 0.0353	0.57; NS
% change in isometric strength	Male	0.09; NS	0.15; NS	1.69; NS	0.46; NS
Baseline whole muscle volume	Male	1.90; NS	0.33; NS	0.98; NS	0.31; NS
Difference in whole muscle volume	Male	1.43; NS	3.43; 0.0345	3.23; 0.0418	0.49; NS

* All models adjusted for age & baseline body mass
** Significance level is 0.0062 after correction for multiple testing.

Continued from p. 24

greater mean baseline subcutaneous fat volume (p=0.0243) than males that were homozygous for the G allele (Table 1). No significant difference in strength or volume was found in females.

The AKT2 rs969531 variant was significantly associated with difference in isometric strength (p=0.0212) and the percent change in isometric strength (p=0.0288) in females, but not in males (Table 2). Females who had a copy of the G allele demonstrated a significantly greater percent change in isometric strength than females that were homozygous for the A allele (Table 1).

TABLE 2. SIGNIFICANT ASSOCIATIONS:

SNP	Phenotype	Gender	F-test	P-value	N; adjusted mean ± SEM	P-value for significantly different means
AKT2 (rs892118)	Difference in whole muscle volume	Male		0.0345	CC (N=117; 70634 ± 4053) CT (N=52; 86995 ± 6083) TT (N=8; 97639 ± 15501)	NONE
AKT2 (rs2304186)	Difference in 1-RM strength	Male	4.20	0.0160	GG (N=104; 10.14 ± 0.48) GT (N=124; 10.97 ± 0.44)* TT (N=60; 8.72 ± 0.64)*	*p=0.0122
AKT2 (rs2304186)	Difference in isometric strength	Male		0.0353	GG (N=103; 19.69 ± 2.02) GT (N=123; 26.06 ± 1.85) TT (N=60; 19.62 ± 2.66)	NONE
AKT2 (rs969531)	Difference in isometric strength	Female		0.0051	GG (N=211; 12.31 ± 0.94)* GA (N=208; 14.58 ± 0.95) AA (N=34; 20.26 ± 2.35)*	*p=0.0054

The AKT2 rs892118 variant was shown to be significantly associated with the difference in whole muscle volume (p=0.0098) and subcutaneous fat volume (p=0.0187) in males (Table 2).

These data suggest that AKT2 genotypes have a sex-specific effect on baseline values of fat in the human arm. Further, AKT2 gene variants play a significant role in increases in muscle strength and size. Further applications of this study will include testing other data sets with similar phenotypes as well as complete functional studies of these AKT2 SNP's in skeletal muscle cells.

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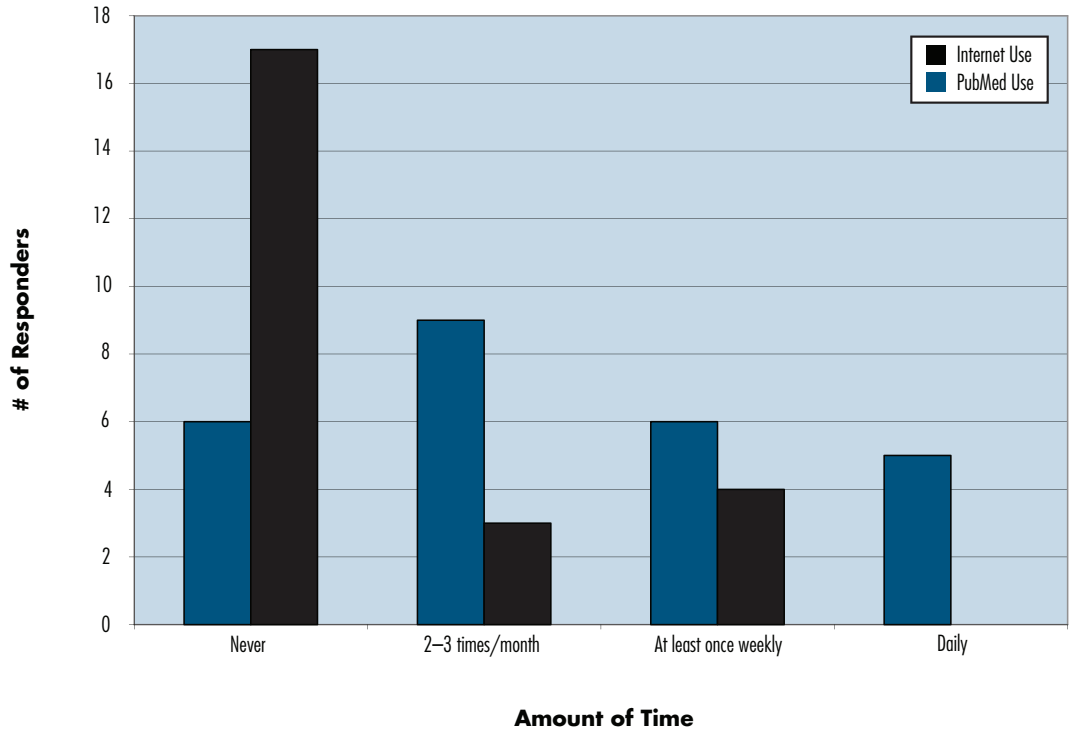
A Needs Assessment of Internet Resource Training of Physicians in Egypt

An essential part of medical education is the use of evidence-based medicine. In April 2009, I participated in a medical mission to Egypt with Hands Along the Nile Development Services (HANDS), facilitated by local partner organization Coptic Evangelical Organization for Social Services (CEOSS), where we held three workshops on navigating through the PubMed MeSH database for 35 physicians in El Minia and Cairo. PubMed was chosen due to its reliability, accessibility, and because it is free of charge. In previous missions, Egyptian physicians voiced a need for internet training, however their level of experience with internet search engines was unclear. Therefore, we decided that this would be an appropriate time to conduct a needs assessment. During each session we administered a pre-test consisting of 15 questions and a post-test consisting of 11 questions to help assess the relevance of our presentation to the physicians. There were, however, limitations of the data collected from the pre- and post-tests, including small sample size, late-comers resulting in more post-test than pre-test responders, and possible misinterpretation of the questions which may explain discrepancy in the data (for example, only 5 of 25 responders stated that they have heard of PubMed, while 7 of 25 stated they had used the database at least weekly).

Each session began with a power-point presentation providing a step-by-step approach to navigating the MeSH database. The remainder of the session involved the participants formulating several questions, using the PICO format, which were then used to search for evidence-based literature through MeSH. PICO is a way of focusing and individualizing a clinical question in order to facilitate a search for relevant evidence-based information. The structure includes:

1. "P" for patient information/characteristics or problem;
2. "I" for interventions, exposures or factors

GRAPH 1: How often do you use internet resources in your practice? How often do you use the PubMed search engine?



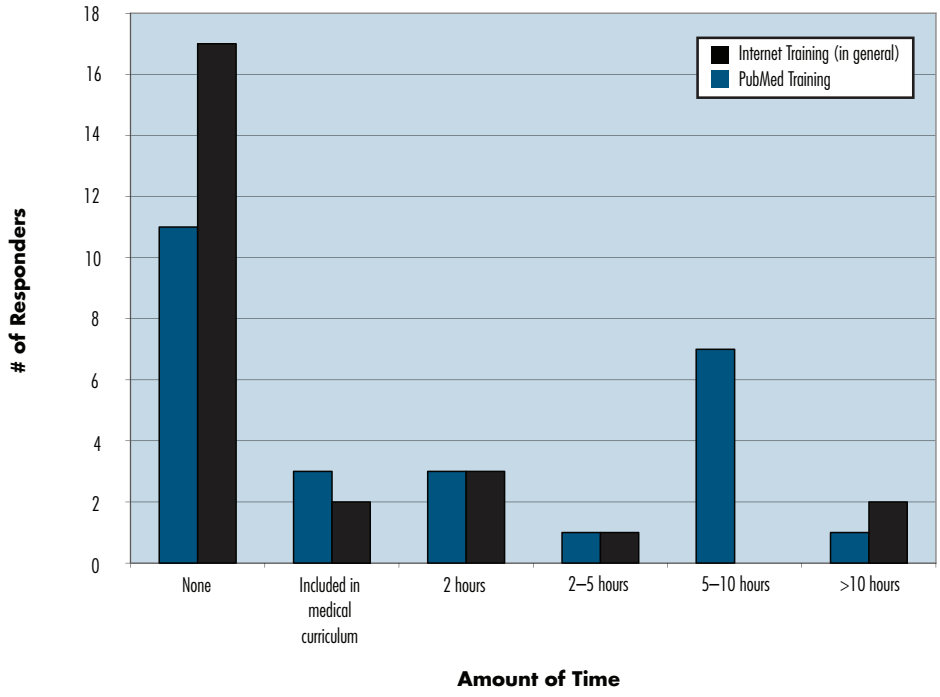
that may influence a prognosis;

3. "C" for comparison if applicable; and
4. "O" for outcome as it is manifested as a change in symptoms, adverse reactions, function or scoring.

Based on information collected from the pre-test, eight of 25 responders had previous training in PubMed [Graph 2], while 7 of 24 had indicated that they have used PubMed at least once a week to search for medically-relevant information [Graph 1]. Although 8 of 20 (40 percent) pre-test responders felt very comfortable in using PubMed, none felt comfortable enough to train others [Graph 4].

By the end of the session, the comfort levels were increased with 20 of 34 (59%) post-test responders indicating that they felt "very comfortable" using MeSH, and with 4 of 34 indicating that they were now "comfortable enough to train others" in the use of PubMed [Graph 4]. Their increasing comfort was also apparent throughout the session as the physicians grew more involved and with many eagerly volunteering to lead different search inquiries. One doctor indicated that "before I depended on my kids to show me how to deal with the net, but now I can [do it on my own]."

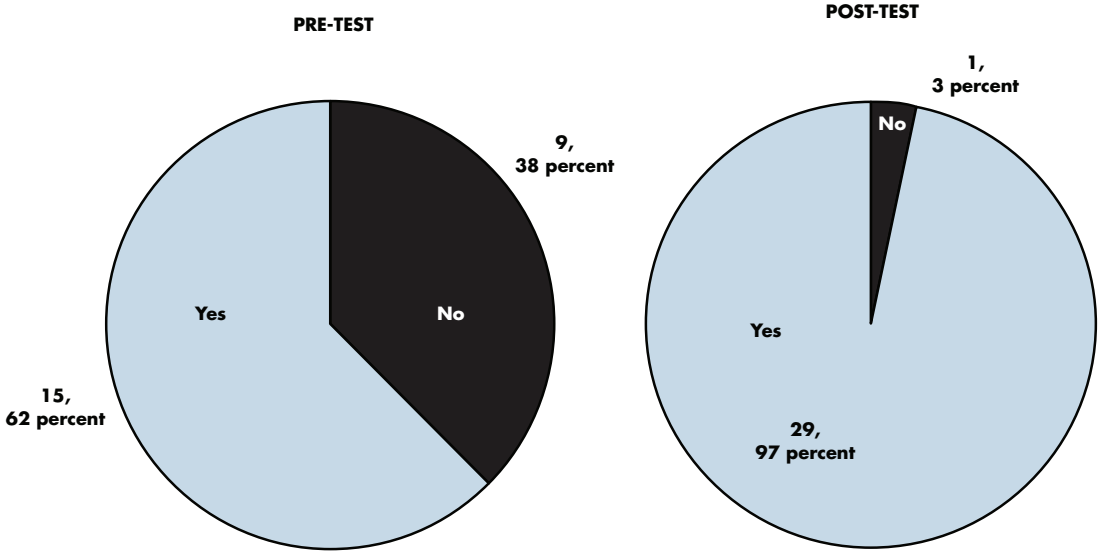
GRAPH 2: How much training have you had in using internet resources (in general)? How many hours of training have you received in using PubMed?



RESOURCE TRAINING

Continued on p. 28

GRAPH 3: Can you define Evidence-Based Medicine?

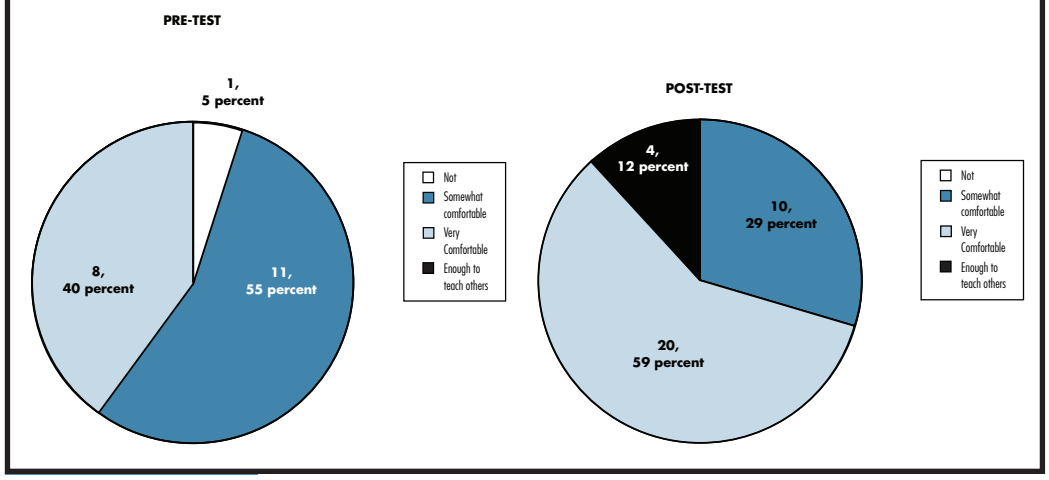


RESOURCE TRAIING

Continued from p. 27

Although the main objective of this presentation was to provide training, we were pleased to find that the physicians were extremely receptive to the material, and that many had taken on a leadership role during the sessions. Some physicians were now able to help their colleagues navigate through the search engine without need for any further assistance. Having resources, other than google, to search for evidence-based literature will allow these doctors to not only update their practices, but will also promote the utilization of evidence-based medicine as they continue to pass this information on to their colleagues.

GRAPH 4: How comfortable are you in using the internet/pubmed to find an evidence-based article?



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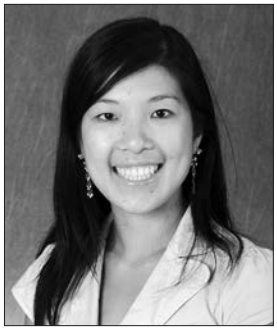

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How Physicians Can Be Effective Injury Prevention Leaders in Gun Safety

Historically, physicians have been involved with injury prevention, such as car safety devices and smoking cessation. Homicide due to firearm injury is the second leading cause of death in the 10–24 age group.[1] In fact, homicide of a household member is three times more likely and suicide risk increases by five times in homes with guns than in homes without guns.[2] Medical societies, such as the American College of Physicians, the American Academy of Pediatricians, and the American Medical Society all support the safe storage of guns.[3]

Out of all health care providers in the United States, pediatricians have the most access to parents.[1] Barkin et al. states that, "because families must bring their children in for routine medical examinations before the children can attend first grade, health professionals have a unique opportunity for early intervention before gun injury, unintentional or intentional, manifests itself."[4] Naureckas et al. found that 25 percent of children between the ages of three and four could pull a trigger of a gun.[5] Jackman et al. found that 76 percent of boys who encounter a gun in a safe environment would handle the gun and 48 percent would pull the trigger.[6] Due to the high risk of mortality from gun violence in children and the decimating impact that death has on loved ones, physicians can play vital roles in health prevention and gun safety.

While most pediatricians believe it is important to counsel patients about gun safety, less than half of them do.[4] There are many surmountable barriers to firearm safety counseling, such as a lack of awareness and prioritization of the issue, insufficient physician knowledge or training, low confidence in the effectiveness counseling, and physician time constraints. Barkin et al. found that "significant positive associations [with firearm safety counseling include] younger clinician age, female sex, household handgun ownership status, and the perception that firearm safety counseling is beneficial."[4] Likewise, Cheng et al. found that "the primary predictors of physician counseling [are] an issue's importance, a physician's perceived self-efficacy,

and perceived effectiveness of counseling, while concerns about time and reimbursement were secondary."[7] Residents [are] more likely to discuss injury prevention and less likely to perceive a barrier if their attending physicians placed importance on this issue.[8] Most patients agree that physicians can influence public opinion, but much fewer think that physicians are knowledgeable in gun safety counseling.[9,10] Even though physicians cite several barriers to injury prevention counseling, patients have confidence in physicians' abilities to change public opinion and consequently, these obstacles can be overcome with the following proposed solutions.[11]

Recommendations for decreasing unintentional injury and death due to guns can be prevented with physician involvement in firearm safety counseling. Cheng et al. stated that "preventive medicine training at all levels, which improves counseling skills and self-efficacy, [is] needed for physicians to attempt counseling and gain experience and confidence."[7] First, increased physician education and exposure to injury prevention training throughout medical school and residency may reinforce the importance of this issue and thus remove several barriers to firearm safety counseling. Second, primary care and pediatric residency programs can teach residents basic information about gun safety and how to research educational information for their patients. Third, physicians can also promote gun safety non-verbally by placing informative brochures in waiting rooms and including questions about gun ownership, exposure, and storage on patient intake forms filled out at each office visit. Everett et al. stated that "interventions aimed at increasing general health promotion activities by physicians [are] successful in increasing physician counseling and [result] in positive changes in their patients' health behaviors…and psychological health."[11] By coupling physician training with patient education, positive public health implications can be achieved.

Previous literature has stated that "the status of physicians' perceptions regarding their ability to impact patients regarding firearm safety is where physicians' perceptions of counseling patients regarding smoking were 25 years ago. The growing crisis in firearm related morbidity and mortality cannot wait another 25 years before the clinical community becomes involved as change agents."[11] Not too long ago, physicians also championed the use of seat belts in cars, thereby decreasing motor vehicle mortalities. Their role as advocates of gun safety is an example of another important public health reform issue with great potential for positive results, which should be addressed now in the midst of our ongoing health care reform.

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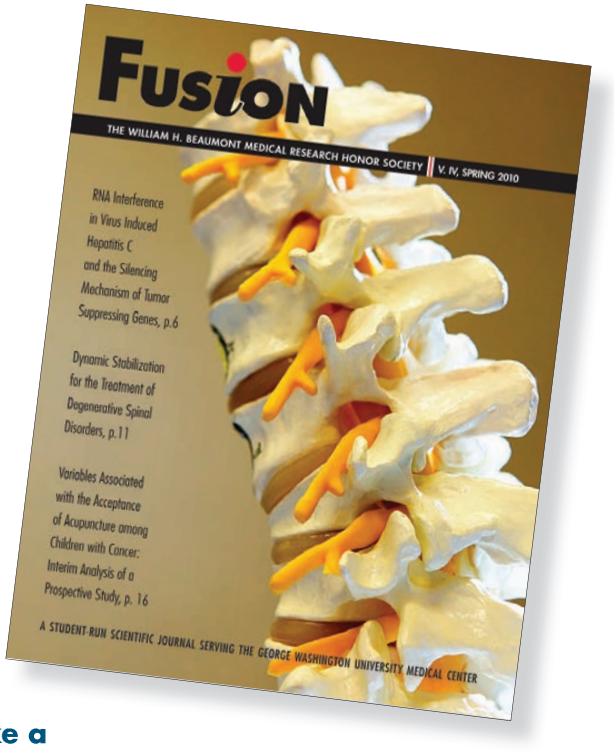

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