

Henry Ford Health System Publication List February 2009

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You can access this page at <http://www.henryfordconnect.com/sliden.cfm?id=436>.

Biostatistics & Research Epidemiology

Strecher, V. J., J. McClure, G. Alexander, B. Chakraborty, V. Nair, J. Konkell, S. Greene, M. Couper, C. Carlier, C. Wiese, R. Little, C. Pomerleau and O. Pomerleau (2008). "The role of engagement in a tailored web-based smoking cessation program: Randomized controlled trial." *J Med Internet Res* **10**(5): 36. [PDF Full-Text](#)

Henry Ford Health System, Detroit, MI

Background: Web-based programs for health promotion, disease prevention, and disease management often experience high rates of attrition. There are 3 questions which are particularly relevant to this issue. First, does engagement with program content predict long-term outcomes? Second, which users are most likely to drop out or disengage from the program? Third, do particular intervention strategies enhance engagement?

Objective: To determine: (1) whether engagement (defined by the number of Web sections opened) in a Web-based smoking cessation intervention predicts 6-month abstinence, (2) whether particular sociodemographic and psychographic groups are more likely to have lower engagement, and (3) whether particular components of a Web-based smoking cessation program influence engagement.

Methods: A randomized trial of 1866 smokers was used to examine the efficacy of 5 different treatment components of a Web-based smoking cessation intervention. The components were: high- versus low-personalized message source, high- versus low-tailored outcome expectation, efficacy expectation, and success story messages. Moreover, the timing of exposure to these sections was manipulated, with participants randomized to either a single unified Web program with all sections available at once, or sequential exposure to each section over a 5-week period of time. Participants from 2 large health plans enrolled to receive the online behavioral smoking cessation program and a free course of nicotine replacement therapy (patch). The program included: an introduction section, a section focusing on outcome expectations, 2 sections focusing on efficacy expectations, and a section with a narrative success story (5 sections altogether, each with multiple screens). Most of the analyses were conducted with a stratification of the 2 exposure types. Measures included: sociodemographic and psychosocial characteristics, Web sections opened, perceived message relevance, and smoking cessation 6-months following quit date.

Results: The total number of Web sections opened was related to subsequent smoking cessation. Participants who were younger, were male, or had less formal education were more likely to disengage from the Web-based cessation program, particularly when the

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program sections were delivered sequentially over time. More personalized source and high-depth tailored self-efficacy components were related to a greater number of Web sections opened. A path analysis model suggested that the impact of high-depth message tailoring on engagement in the sequentially delivered Web program was mediated by perceived message relevance.

Conclusions: Results of this study suggest that one of the mechanisms underlying the impact of Web-based smoking cessation interventions is engagement with the program. The source of the message, the degree of message tailoring, and the timing of exposure appear to influence Web-based program engagement.

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Biostatistics & Research Epidemiology

Wegienka, G., S. Havstad, E. M. Zoratti, D. R. Ownby and C. C. Johnson (2009).

"Association of early life wheeze and lung function." Ann Allergy Asthma Immunol **102**(1): 29-34. [PDF Full-Text](#)

Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, MI
gwegien1@hfhs.org

BACKGROUND: The incidence of wheeze is unknown and the role of early life wheeze in subsequent health is not clearly understood. OBJECTIVE: To calculate the age-specific incidence of wheeze and determine whether wheezing at particular times in early life was predictive of abnormal airway hyperresponsiveness (AHR), percentage of predicted forced expiratory volume in 1 second (FEV1), and current asthma at the age of 6 years. METHODS: Using data from a birth cohort study with annual report of wheezing (Childhood Allergy Study) and spirometry and methacholine challenge at the age of 6 years, the age-specific incidence of wheeze was determined using Kaplan-Meier estimates. Logistic and linear regression models were used to assess the associations between the presence of age-specific wheezing and the outcomes of current asthma, AHR, and percentage of predicted FEV1 at the age of 6 years. RESULTS: A total of 724 children had parents who completed at least the first annual interview and were therefore included in the study. The 6-year cumulative incidence of wheezing was higher for boys (66.2%; 95% confidence interval, 59.8%- 72.6%) than for girls (47.6%; 95% confidence interval, 41.4%-53.8%). There was no age when wheezing was more strongly associated with either AHR or percentage of predicted FEV1 at 6 years. Only wheeze in the fifth year among boys and wheezing in both the fourth and fifth years in girls were positively predictive of current asthma at the age of 6 years. This is likely because of the definition of current asthma (ever physician diagnosis and either medication or symptoms in last year). Eczema, parental asthma history, and total cord blood IgE did not affect these associations. CONCLUSIONS: Wheezing at any particular time in early life may not be predictive of early childhood lung function.

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Biostatistics & Research Epidemiology

Alford, S. H., K. Schwartz, A. Soliman, C. C. Johnson, S. B. Gruber and S. D. Merajver (2009). "Breast cancer characteristics at diagnosis and survival among Arab-American women compared to European- and African-American women." Breast Cancer Res Treat **114**(2): 339-46. [Article Request Form](#)

Henry Ford Hospital, Detroit, MI

BACKGROUND: Data from Arab world studies suggest that Arab women may experience a more aggressive breast cancer phenotype. To investigate this finding, we focused on one of the largest settlements of Arabs and Iraqi Christians (Chaldeans) in the US, metropolitan Detroit- a SEER reporting site since 1973. MATERIALS AND METHODS: We identified a cohort of primary breast cancer cases diagnosed 1973-2003. Using a validated name algorithm, women were identified as being of Arab/Chaldean descent if they had an Arab last or maiden name. We compared characteristics at diagnosis (age, grade, histology, SEER stage, and marker status) and overall survival between Arab-, European-, and African-Americans. RESULTS: The cohort included 1,652 (2%) women of Arab descent, 13,855 (18%) African-American women, and 63,615 (80%) European-American women. There were statistically significant differences between the racial groups for all characteristics at diagnosis. Survival analyses overall and for each SEER stage showed that Arab-American women had the best survival, followed by European-American women. African-American women had the

poorest overall survival and were 1.37 (95% confidence interval: 1.23-1.52) times more likely to be diagnosed with an aggressive tumor (adjusting for age, grade, marker status, and year of diagnosis). CONCLUSION: Overall, Arab-American women have a distribution of breast cancer histology similar to European-American women. In contrast, the stage, age, and hormone receptor status at diagnosis among Arab-Americans was more similar to African-American women. However, Arab-American women have a better overall survival than even European-American women.

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Bone & Joint Center

Anderst, W., R. Zauel, J. Bishop, E. Demps and S. Tashman (2009). "Validation of three-dimensional model-based tibio-femoral tracking during running." *Med Eng Phys* **31**(1): 10-16. [Article Request Form](#)

Henry Ford Hospital, Bone & Joint Center, Detroit, MI 48202

The purpose of this study was to determine the accuracy of a radiographic model-based tracking technique that measures the three-dimensional in vivo motion of the tibio-femoral joint during running. Tantalum beads were implanted into the femur and tibia of three subjects and computed tomography (CT) scans were acquired after bead implantation. The subjects ran 2.5 m/s on a treadmill positioned within a biplane radiographic system while images were acquired at 250 frames per second. Three-dimensional implanted bead locations were determined and used as a "gold standard" to measure the accuracy of the model-based tracking. The model-based tracking technique optimized the correlation between the radiographs acquired via the biplane X-ray system and digitally reconstructed radiographs created from the volume-rendered CT model. Accuracy was defined in terms of measurement system bias, precision and root-mean-squared (rms) error. Results were reported in terms of individual bone tracking and in terms of clinically relevant tibio-femoral joint translations and rotations (joint kinematics). Accuracy for joint kinematics was as follows: model-based tracking measured static joint orientation with a precision of 0.2 degrees or better, and static joint position with a precision of 0.2 mm or better. Model-based tracking precision for dynamic joint rotation was 0.9 +/- 0.3 degrees, 0.6 +/- 0.3 degrees, and 0.3 +/- 0.1 degrees for flexion-extension, external-internal rotation, and ab-adduction, respectively. Model-based tracking precision when measuring dynamic joint translation was 0.3 +/- 0.1 mm, 0.4 +/- 0.2 mm, and 0.7 +/- 0.2 mm in the medial-lateral, proximal-distal, and anterior-posterior direction, respectively. The combination of high-speed biplane radiography and volumetric model-based tracking achieves excellent accuracy during in vivo, dynamic knee motion without the necessity for invasive bead implantation.

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Bone & Joint Center

Drum, M. G., C. M. Les, R. D. Park, R. W. Norrdin, C. W. McIlwraith and C. E. Kawcak (2009). "Correlation of quantitative computed tomographic subchondral bone density and ash density in horses." *Bone* **44**(2): 316-9. [PDF Full-Text](#)

Henry Ford Hospital, Bone and Joint Center, Detroit, MI

The purpose of this study was to compare subchondral bone density obtained using quantitative computed tomography with ash density values from intact equine joints, and to determine if there are measurable anatomic variations in mean subchondral bone density. Five adult equine metacarpophalangeal joints were scanned with Computed tomography (CT), disarticulated, and four 1-cm(3) regions of interest (ROI) cut from the distal third metacarpal bone. Bone Cubes were ashed, and percent mineralization and ash density were recorded. Three-dimensional models were created of the distal third metacarpal bone from CT images. Four ROIs were measured on the distal aspect of the third metacarpal bone at axial and abaxial sites of the medial and lateral condyles for correlation with ash samples. Overall correlations of mean quantitative CT (QCT) density with ash density ($r=0.82$) and percent mineralization ($r=0.93$) were strong. There were significant differences between abaxial and axial ROIs for mean QCT density, percent bone mineralization and ash density ($p<0.05$). QCT appears to be a good measure of bone density in equine subchondral bone. Additionally, differences existed between axial and abaxial subchondral bone density in the equine distal third metacarpal bone.

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Cardiology

Al-Mallah, M., F. Alqaisi, D. Nerenz, S. Boedeker and W. D. Weaver (2008). "Does public smoking ban reduce the incidence of myocardial infarction in Michigan? A systematic review and attributal risk analysis." Circulation **118**(18 Suppl 2): S1148.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Hospital, Detroit, MI

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Cardiology

Armstrong, P. W., Y. L. Fu, C. M. Westerhout, H. D. White, M. P. Hudson, K. W. Mahaffey, T. G. Todaro, P. E. Aylward and C. G. Granger (2008). "Baseline Q trumps time from symptom onset as a prognostic marker in STEMI patients treated with primary PCI." Circulation **118**(18 Suppl 2): S1076.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Hospital, Detroit, MI

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Cardiology

Borges-Neto, S., A. E. Iskandrian, D. J. Whellan, C. M. O'Connor, S. J. Ellis, R. Pagnanelli, S. Settles, A. Kao, K. Abdul-Nour, W. Kraus, G. Ewald and D. Kitzman (2008). "Effect of exercise training on myocardial perfusion, function and dyssynchrony, in heart failure patients: A sub-study of the HF-ACTION Trial." Circulation **118**(18 Suppl 2): S1028.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Hospital, Detroit, MI

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Cardiology

Duda, M. K., K. M. O'Shea, A. Tintinu, W. H. Xu, R. J. Khairallah, B. R. Barrows, D. J. Chess, A. M. Azimzadeh, W. S. Harris, V. G. Sharov, H. N. Sabbah and W. C. Stanley (2009). "Fish oil, but not flaxseed oil, decreases inflammation and prevents pressure overload-induced cardiac dysfunction." Cardiovasc Res **81**(2): 319-27. [PDF Full-Text](#)

Henry Ford Hospital, Henry Ford Heart & Vascular Institute, Division of Cardiovascular Medicine, Detroit, MI 48202

Clinical studies suggest that intake of omega-3 polyunsaturated fatty acids (omega-3 PUFA) may lower the incidence of heart failure. Dietary supplementation with omega-3 PUFA exerts metabolic and anti-inflammatory effects that could prevent left ventricle (LV) pathology; however, it is unclear whether these effects occur at clinically relevant doses and whether there are differences between omega-3 PUFA from fish [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] and vegetable sources [alpha-linolenic acid (ALA)].

We assessed the development of LV remodelling and pathology in rats subjected to aortic banding treated with omega-3 PUFA over a dose range that spanned the intake of humans taking omega-3 PUFA supplements.

Rats were fed a standard food or diets supplemented with EPA+DHA or ALA at 0.7, 2.3, or 7% of energy intake. Without supplementation, aortic banding increased LV mass and end-systolic and -diastolic volumes. ALA supplementation had little effect on LV remodelling and dysfunction. In contrast, EPA+DHA dose-dependently increased EPA and DHA, decreased arachidonic acid in cardiac membrane phospholipids, and prevented the increase in LV end-diastolic and -systolic volumes. EPA+DHA resulted in a dose-dependent increase in the anti-inflammatory adipokine adiponectin, and there was a strong correlation between the prevention of LV chamber enlargement and plasma levels of adiponectin ($r = -0.78$). Supplementation with EPA+DHA had anti-aggregatory and anti-inflammatory effects as evidenced by decreases in urinary thromboxane B-2 and serum tumour necrosis factor-alpha.

Dietary supplementation with omega-3 PUFA derived from fish, but not from vegetable sources, increased plasma adiponectin, suppressed inflammation, and prevented cardiac remodelling and dysfunction under pressure overload conditions.

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Cardiology

Gupta, R. C., S. Mishra, M. Wang, A. Jiang, S. Rastogi, B. Rousso, Y. Mika and H. N. Sabbah (2009). "Cardiac contractility modulation electrical signals normalize activity, expression, and phosphorylation of the Na⁺-Ca²⁺ exchanger in heart failure." J Card Fail **15**(1): 48-56. [PDF Full-Text](#)

Department of Medicine, Division of Cardiovascular Medicine, Henry Ford Heart and Vascular Institute, Detroit, Michigan 48202, USA.

BACKGROUND: Expression and phosphorylation of the cardiac Na⁽⁺⁾-Ca⁽²⁺⁾ exchanger-1 (NCX-1) are up-regulated in heart failure (HF). We examined the effects of chronic cardiac contractility modulation (CCM) therapy on the expression and phosphorylation of NCX-1 and its regulators GATA-4 and FOG-2 in HF dogs. **METHODS AND RESULTS:** Studies were performed in LV tissue from 7 CCM-treated HF dogs, 7 untreated HF dogs, and 6 normal (NL) dogs. mRNA expression of NCX-1, GATA-4, and FOG-2 was measured using reverse transcriptase polymerase chain reaction, and protein level was determined by Western blotting. Phosphorylated NCX-1 (P-NCX) was determined using a phosphoprotein enrichment kit. Compared with NL dogs, NCX-1 mRNA and protein expression and GATA-4 mRNA and protein expression increased in untreated HF dogs, whereas FOG-2 expression decreased. Compared with NL dogs, the level of P-NCX-1 normalized to total NCX-1 increased in untreated HF dogs (0.80±/0.10 vs 0.37±/0.04; $P < .05$). CCM therapy normalized NCX-1 expression, GATA-4, and FOG-2 expression, and the ratio of P-NCX-1 to total NCX-1 (0.62±/0.10). **CONCLUSION:** Chronic monotherapy with CCM restores expression and phosphorylation of NCX-1. These findings are consistent with previous observations of improved LV function and normalized sarcoplasmic reticulum calcium cycling in the left ventricles of HF dogs treated with CCM therapy.

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Cardiology

Khan, A., R. Nair and C. Schuger (2009). "Focal Atrial Tachycardia Originating from the Right Hepatic Vein." J Cardiovasc Electrophysiol. Epub Ahead of Print. [PDF Full-Text](#)

From the Henry Ford Hospital, Department of Cardiac Electrophysiology, Detroit, Michigan, USA.

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Cardiology

Lanfear, D., R. C. Gupta, R. N. Bazari, R. Hasan, C. Williams, B. Czerska, C. Tita and H. N. Sabbah (2008). "Short term effects of milrinone on biomarkers in severe heart failure." Circulation **118**(18 Suppl 2): S723.

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Henry Ford Hospital, Detroit, MI

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Cardiology

Lanfear, D. E., P. G. Jones, S. Cresci, F. Tang, S. S. Rathore and J. A. Spertus (2008). "Patient willingness to participate in genetic research after a myocardial infarction." Circulation **118**(18 Suppl 2): S624.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Hospital, Detroit, MI

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Cardiology

Reynolds, M. R., A. D. Kugelmass, P. P. Brown, S. D. Culler and A. W. Simon (2008). "Financial impact to hospitals of changing Medicare payment policy for avoidable complications associated with cardiovascular admissions." Circulation **118**(18): S1119.

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Henry Ford Hospital, Detroit, MI

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Cardiology

Wang, M., V. Zaca, A. Jiang, I. Ilisar, M. Ebinger, H. B. Sabbah, K. Dye, C. Schuger and H. N. Sabbah (2008). "Long-term baroreflex activation therapy increases the threshold for the induction of lethal ventricular arrhythmias in gos with chronic advanced heart failure." Circulation **118**(18 Suppl 2): S722.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Hospital, Detroit, MI

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Cardiology

Xu, J., O. A. Carretero, E. G. Shesely, T. L. Reudelhuber and X. P. Yang (2008). "Angiotensin II overexpression in the heart: Effect on cardiac function and remodeling in deoxycorticosterone acetate-salt hypertension." Circulation **118**(18, Suppl 2): S285-6.

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Henry Ford Hospital, Detroit, MI 48202

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Cardiology

Yeo, K. K., Z. M. Li, S. Katz, J. Douketis, B. Danielsen and R. H. White (2008). "Risk of stroke after new-onset atrial fibrillation versus chronic AF in patients undergoing coronary artery bypass surgery." Circulation **118**(18 Suppl 2): S1119.

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Henry Ford Hospital, Detroit, MI

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Cardiology

Zhang, Y. H., I. Ilsar, H. N. Sabbah, T. B. David and T. N. Mazgalev (2009). "Relationship between right cervical vagus nerve stimulation and atrial fibrillation inducibility: Therapeutic intensities do not increase arrhythmogenesis." Heart Rhythm 6(2): 244-50. [Article Request Form](#)

Henry Ford Health System, Detroit, MI

BACKGROUND Strong vagus nerve stimulation (VNS) is routinely used to induce and maintain atrial fibrillation (AF) in acute animal studies. Taken as a surrogate of increased vagal tone, such observations suggest an arrhythmogenic role of VNS in AF. In contrast, VNS has been demonstrated to have profound therapeutic effects in heart failure and other ailments.

OBJECTIVE The purpose of this study was to examine the relationship between right cervical VNS and AF, especially the potential arrhythmogenic effects of therapeutic VNS.

METHODS The relationship between VNS intensities and AF inducibility was studied in eight acute dogs at baseline and four different Levels of VNS, which were set to prolong spontaneous sinus cycle Length (SCL) by 20%, 40%, 60%, or 100%. The effect of mild VNS treatment on AF induction was further investigated in six chronically instrumented conscious dogs. These dogs were implanted with right cervical VNS stimulators and specialized atrial pacemakers. VNS intensity was titrated to slow the sinus rate by 10%.

RESULTS In acute studies, it was found that mild to moderate VNS (i.e., producing $\leq 40\%$ SCL prolongation) did not increase AF inducibility, while strong VNS (i.e., producing $\geq 60\%$ SCL prolongation) did. In chronic studies, compared with controls, AF induction did not change during the 4-week VNS treatment.

CONCLUSIONS AF inducibility by right cervical VNS is intensity dependent: strong VNS (producing $\geq 60\%$ SCL prolongation) facilitates AF, while moderate VNS (producing $\leq 40\%$ SCL prolongation) appears not to affect AF. The nonarrhythmogenic effect of therapeutic chronic VNS was further verified in conscious animals. We conclude that VNS with moderate intensities can be used to deliver therapeutic benefits without arrhythmogenic risk.

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Center for Health Promotion & Disease Prevention

Milberger, S., R. M. Davis and A. L. Holm (2009). "Pet Owners' Attitudes and Behaviors Related to Smoking and Secondhand Smoke: A Pilot Study." Tob Control. Epub Ahead of Print. [PDF Full-Text](#)

Henry Ford Health System, United States.

BACKGROUND: Although research indicates that secondhand smoke (SHS) harms both human and animal health, data on the percentage of pet owners who smoke or allow smoking in their homes are not readily available. **OBJECTIVE:** To investigate pet owners' smoking behavior and policies on smoking in their homes, and the potential for educational interventions to motivate change in pet owners' smoking behavior. **METHOD:** A web-based survey was used with 3,293 adult pet owners. The main outcome measures were smoking behavior of pet owners and their cohabitants; policies on smoking in pet owners' homes; and impact of information about the dangers of pet exposure to SHS on pet owners' smoking intentions. **RESULTS:** Twenty-one percent of respondents were current smokers and 27% of participants lived with at least one smoker. Pet owners who smoke reported that information on the dangers of pet exposure to SHS would motivate them to try to quit smoking (28.4%) and ask the people with whom they live to quit smoking (8.7%) or not to smoke indoors (14.2%). Moreover, non-smoking pet owners who live with smokers said that they would ask the people with whom they live to quit (16.4%) or not smoke indoors (24.2%) if given this information. About 40%

of current smokers and 24% of non-smokers living with smokers indicated that they would be interested in receiving information on smoking, quitting, or SHS. CONCLUSION: Educational campaigns informing pet owners of the risks of SHS exposure for pets could motivate some pet owners to quit smoking. It could also motivate these owners and non-smoking owners who cohabit with smokers make their homes smoke-free.

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Dermatology

Eide, M. J., M. A. Weinstock and M. A. Clark (2009). "Demographic and socioeconomic predictors of melanoma prognosis in the United States." J Health Care Poor Underserved **20**(1): 227-45. [Article Request Form](#)

Department of Community Health, Brown University, Center for Gerontology and Healthcare Research, Providence, RI, USA. meide1@hfh.org

Studies suggest sociodemographic factors may influence melanoma prognosis. Our objective was to quantify sociodemographic predictors of U.S. melanoma. Data from 17,702 melanoma cases reported to the Surveillance Epidemiology and End Results (SEER) program from 1988-1993 were merged with sociodemographic data (1990 U.S. Census). Regression analysis was used to model prognosis: melanoma mortality to incidence ratio. Prognosis was significantly associated with neighborhood racial heterogeneity, education and income. Melanoma patients who resided in areas with higher education (OR 0.4, 95% CI 0.3-0.5), more White residents (OR 0.7, 95% CI 0.5-0.8), or higher incomes (OR 0.4, 95% CI 0.2-0.5) were less likely to have poor prognosis. Education explained 3.3 times more variance than race and 1.9 times more than income. Sociodemographic factors were associated with stage and tumor thickness. Neighborhood sociodemographic variables were predictive of melanoma prognosis, and suggest an important direction for targeting public health efforts to reach those in at-risk communities.

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Dermatology

Hornyak, T. J., S. Jiang, E. A. Guzman, B. N. Scissors, C. Tuchinda, H. He, J. D. Neville and F. M. Strickland (2009). "Mitf Dosage as a Primary Determinant of Melanocyte Survival after UV Irradiation." Pigment Cell Melanoma Res. EPub Ahead of Print. [Article Request Form](#)

Department of Dermatology, One Ford Place 4D, Henry Ford Health System, Detroit, MI, 48202 USA.

Summary - Microphthalmia-associated transcription factor (Mitf) is essential for melanocyte development and function and regulates anti-apoptotic Bcl2 expression. We hypothesized that cellular deficiency of Mitf can influence melanocyte survival in response to ultraviolet (UV) radiation. Primary melanocyte cultures were prepared from neonatal wild-type mice and congenic animals heterozygous for Mitf mutations Mitf(mi-vga9/+) and Mitf(Mi-wh/+) and exposed to UV irradiation. Wild-type melanocytes were more resistant to UV-induced apoptosis than melanocytes partially deficient in Mitf activity, as determined by relative levels of intracellular melanin and relative activation of Mitf target genes Tyr, Tyrp1, Dct, and Cdk2. Comparative experiments with wild-type cells and congenic albino melanocytes demonstrated that these differences are not due to differences in melanin content, implicating Mitf as a primary determinant of UV-dependent melanocyte survival. Mitf activity correlated directly with resistance to UV-induced apoptosis in melanocytes. Mitf was important not only for regulating the expression of anti-apoptotic Bcl-2 following UV irradiation, but also the expression of the pro-apoptotic BH3-only Bad protein and activation of the extrinsic apoptotic pathway. Hence, Mitf is a multifaceted regulator of UV-induced apoptosis in melanocytes.

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Dermatology

Tierney, E. P., C. W. Hanke and A. B. Kimball (2009). "Recent Changes in the Workforce and Practice of Dermatologic Surgery." Dermatol Surg. EPub Ahead of Print. [PDF Full-Text](#)

Department of Dermatology, Henry Ford Health System, Detroit, Michigan;

BACKGROUND The increasing number of American College of Mohs Surgery (ACMS) fellowship positions over the last decade has resulted in a greater number of fellowship-trained surgeons in dermatologic surgery. **METHODS** Mohs micrographic fellowship-trained surgeons (MMFTSs) and non-Mohs fellowship-trained surgeons performing Mohs micrographic surgery (NMMFTSs) were compared using the American Academy of Dermatology Practice Profile Survey (2002/05). An analysis of recent Mohs fellowship classes was also performed. **RESULTS** In 2005, there was an equivalent proportion of MMFTSs and NMMFTSs in the workforce (ratio MMFTS:NMMFTS=0.9) but, in 2005, there was a shift in the youngest age cohort (29-39) to a greater proportion of MMFTSs (MMFTS:NMMFTS=1.55). In 2005, the youngest MMFTSs (29-39) were more likely to be female (47.1%) than of MMFTSs overall (24%). MMFTSs were 5 times as likely to be in full-time academic positions and performed 2 to 3 times as many Mohs cases per week as NMMFTSs. **CONCLUSIONS** Consistent with demographic shifts in dermatology, differences have emerged in the demographics, surgical volumes, and settings of MMFTSs and NMMFTSs. Recent increases in the ACMS fellowship positions have resulted in a greater proportion of MMFTSs among younger dermatologic surgeons. It will be important to follow how this increase in fellowship trainees affects the dermatologic surgery workforce. The authors have indicated no significant interest with commercial supporters.

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Dermatology

Tierney, E. P., R. L. Moy and D. J. Kouba (2009). "Rapid absorbing gut suture versus 2-octylethylcyanoacrylate tissue adhesive in the epidermal closure of linear repairs." J Drugs Dermatol **8**(2): 115-9.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Department of Dermatology, Henry Ford Health System, Detroit, MI 48204, USA.

BACKGROUND: While a variety of epidermal wound closure techniques are utilized, there are few evidence based studies comparing techniques in head-to-head studies. **OBJECTIVE:** To compare the aesthetic outcomes and wound healing properties of 2 epidermal closure mechanisms: 2-octylethylcyanoacrylate adhesive and rapid absorbing gut suture in skin closures. **METHODS:** A total of 8 patients were enrolled in this randomized right-left comparative trial. Patients were randomized for epidermal closure with one half of their wounds (chest [n=6] and upper extremities [n=2]) with tissue adhesive and the contralateral with rapid absorbing gut suture. **RESULTS:** Three months following wound closure, overall cosmetic outcome was slightly greater on the half closed with rapid absorbing gut suture (mean=3.56) relative to the tissue adhesive (mean=3.19, P=.05). For dyspigmentation, the half of the scar treated with the suture had a better outcome (mean=3.50) relative to tissue adhesive (mean=2.75) (P<.05). All other variables (i.e., scar thickness, wound approximation, patient outcome, and preference) were highly equivalent. **CONCLUSION:** Both rapid absorbing gut suture and tissue adhesive appear to be highly efficacious techniques for epidermal closure. It appears that tissue adhesive may not be as effective in achieving optimal cosmesis for defects after Mohs micrographic surgery on the trunk and extremities in follow-up at 3 months.

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Dermatology

Zhou, L., H. Z. He, J. X. Mi, C. G. Li, B. Lee and Q. S. Mi (2008). "MicroRNA genes are they susceptibility candidates for human type 1 diabetes?" Ann N Y Acad Sci / Immunology of Diabetes V: From Bench to Bedside **1150**: 72-5. [PDF Full-Text](#)

Henry Ford Hospital, Program Immunology, Department of Dermatology, Detroit, MI 48202

Human type 1 diabetes (T1D) is a chronic autoimmune disorder with complex genetic inheritance. To date, more than 19 insulin-dependent diabetes mellitus (IDDM) susceptibility loci have been mapped to specific chromosome regions in the human. MicroRNAs (miRNAs) are a recently discovered class of evolutionarily conserved small noncoding RNAs that negatively regulate the expression of protein-coding genes without affecting mRNA levels. There are a growing number of reports that miRNAs link to the regulation of different biological pathways associated with human diseases. However, the potential role of miRNAs in human T1D is

still unknown. To investigate the possible involvements of miRNAs in human T1D on a genome-wide basis, we have mapped 530 miRNAs and compared their locations to the current IDDM loci. We found that at least 27 miRNAs are located in 9 human IDDM loci. More interestingly, some of them potentially target autoimmune- and beta-cell-related genes. Our data represent a genome-wide search for a potential correlation between the genomic position of miRNAs and specific IDDM loci, indicating that miRNAs may be susceptibility candidates or biomarkers for human T1D.

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Diagnostic Radiology

Ertl-Wagner, B. B., J. D. Blume, D. Peck, J. K. Udupa, B. Herman, A. Levering and I. M. Schmalfluss (2009). "Reliability of tumor volume estimation from MR images in patients with malignant glioma. Results from the American College of Radiology Imaging Network (ACRIN) 6662 Trial." Eur Radiol **19**(3): 599-609. [PDF Full-Text](#)

Henry Ford Hospital, Department of Radiology, Detroit, MI

Reliable assessment of tumor growth in malignant glioma poses a common problem both clinically and when studying novel therapeutic agents. We aimed to evaluate two software-systems in their ability to estimate volume change of tumor and/or edema on magnetic resonance (MR) images of malignant gliomas. Twenty patients with malignant glioma were included from different sites. Serial post-operative MR images were assessed with two software systems representative of the two fundamental segmentation methods, single-image fuzzy analysis (3DVIEWNIX-TV) and multi-spectral-image analysis (Eigentool), and with a manual method by 16 independent readers (eight MR-certified technologists, four neuroradiology fellows, four neuroradiologists). Enhancing tumor volume and tumor volume plus edema were assessed independently by each reader. Intraclass correlation coefficients (ICCs), variance components, and prediction intervals were estimated. There were no significant differences in the average tumor volume change over time between the software systems ($p > 0.05$). Both software systems were much more reliable and yielded smaller prediction intervals than manual measurements. No significant differences were observed between the volume changes determined by fellows/neuroradiologists or technologists. Semi-automated software systems are reliable tools to serve as outcome parameters in clinical studies and the basis for therapeutic decision-making for malignant gliomas, whereas manual measurements are less reliable and should not be the basis for clinical or research outcome studies.

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Diagnostic Radiology

Soleymani, M., G. A. Hossein-Zadeh and H. Sotanian-Zadeh (2009). "Fixed and random effect analysis of multi-subject fMRI data using wavelet transform." J Neurosci Methods **176**(2): 237-45. [Article Request Form](#)

Henry Ford Hospital, Department of Radiology, Image Analysis Lab, Detroit, MI 48202

We propose a new method to estimate the random effect variance in group analysis of fMRI data. In the first level of analysis, general linear model (GLM) is used to estimate a parameter map ("effect") for each subject. After applying discrete wavelet transform to the "effect" maps, noise is reduced through a vertical energy thresholding (VET). The fixed effect component in each coefficient is derived by averaging the wavelet coefficients along all subjects. Then, the wavelet coefficients containing significant random effect are identified by their higher sample variance along the subjects. Wavelet coefficients containing random effect component in each subject are used to reconstruct the random effect maps through an inverse wavelet transform. Random effect variance is obtained from random effect maps for use in random effect analysis. The proposed method and other methods like GLM group analysis and variance ratio smoothing are applied to both experimental and artificial fMRI data. ROC curves, obtained from the simulated data, show improved group activation detection compared to existing random effect analysis methods. For the experimental data, the proposed method shows its high sensitivity by detecting multiple activation regions, namely visual cortex, cuneus, precuneus, thalamus, and cerebellum. From these regions, precuneus and cerebellum are not detected by majority of the previously published methods.

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Emergency Medicine

Boehm, K. M. and A. Pugh (2009). "A new variant of Witiitis." J Emerg Med **36**(1): 80. [PDF Full-Text](#)

Henry Ford Wyandotte Hospital, Department of Emergency Medicine, Wyandotte, MI

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Endocrinology & Metabolism

Danescu, L. G., S. Levy and J. Levy (2009). "Vitamin D and diabetes mellitus." Endocrine **35**(1): 11-7. [Article Request Form](#)

Henry Ford Hospital, Division of Endocrinology, Detroit, MI 48202

Better understanding of the physiological role of the vitamin-D system, in particular its potential effects on inflammatory and autoimmune conditions as well as on insulin secretion and possibly also on insulin resistance, increased the interest in its potential role in prevention and control of the diabetic condition, both type-1 and -2 diabetes. Both these conditions are associated with inflammation and type-1 diabetes also with an autoimmune pathology. Indeed, animal and human studies support the notion that adequate vitamin-D supplementation may decrease the incidence of type-1 and possibly also of type-2 diabetes mellitus and may improve the metabolic control in the diabetes state. However, the exact mechanisms by which vitamin-D and calcium supplementation exert their beneficial effects are not clear and need further investigation.

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Endocrinology & Metabolism

Eastell, R., A. Arnold, M. L. Brandi, E. M. Brown, P. D'Amour, D. A. Hanley, D. S. Rao, M. R. Rubin, D. Goltzman, S. J. Silverberg, S. J. Marx, M. Peacock, L. Mosekilde, R. Bouillon and E. M. Lewiecki (2009). "Diagnosis of asymptomatic primary hyperparathyroidism: Proceedings of the Third International Workshop." J Clin Endocrinol Metab **94**(2): 340-50. [PDF Full-Text](#)

Henry Ford Hospital, Bone & Mineral Research Lab, Detroit, MI 48202

Objective: Asymptomatic primary hyperparathyroidism (PHPT) is a common clinical problem. The purpose of this report is to guide the use of diagnostic tests for this condition in clinical practice.

Participants: Interested professional societies selected a representative for the consensus committee and provided funding for a one-day meeting. A subgroup of this committee set the program and developed key questions for review. Consensus was established at a closed meeting that followed. The conclusions were then circulated to the participating professional societies.

Evidence: Each question was addressed by a relevant literature search (on PubMed), and the data were presented for discussion at the group meeting.

Consensus Process: Consensus was achieved by a group meeting. Statements were prepared by all authors, with comments relating to accuracy from the diagnosis subgroup and by representatives from the participating professional societies.

Conclusions: We conclude that: 1) reference ranges should be established for serum PTH in vitamin D-replete healthy individuals; 2) second-and third-generation PTH assays are both helpful in the diagnosis of PHPT; 3) DNA sequence testing can be useful in familial hyperparathyroidism or hypercalcemia; 4) normocalcemic PHPT is a variant of the more common presentation of PHPT with hypercalcemia; 5) serum 25-hydroxyvitamin D levels should be measured and, if vitamin D insufficiency is present, it should be treated as part of any management course; and 6) the estimated glomerular filtration rate should be used to determine the level of kidney function in PHPT: an estimated glomerular filtration rate of less than 60 ml/min . 1.73 m(2) should be a benchmark for decisions about surgery in established asymptomatic PHPT.

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Eye Care Services

Diabetic Retinopathy Clinical Research Group (2009). "Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings." *Arch Ophthalmol* **127**(2): 132-40. [PDF Full-Text](#)

Objective: To compare the effects of single-sitting vs 4-sitting panretinal photocoagulation (PRP) on macular edema in subjects with severe nonproliferative or early proliferative diabetic retinopathy with relatively good visual acuity and no or mild center-involved macular edema.

Methods: Subjects were treated with 1 sitting or 4 sittings of PRP in a nonrandomized, prospective, multicentered clinical trial.

Main Outcome Measure: Central subfield thickness on optical coherence tomography (OCT).

Results: Central subfield thickness was slightly greater in the 1-sitting group (n = 84) than in the 4-sitting group (n = 71) at the 3-day (P = .01) and 4-week visits (P = .003). At the 34-week primary outcome visit, the slight differences had reversed, with the thickness being slightly greater in the 4-sitting group than in the 1-sitting group (P = .06). Visual acuity differences paralleled OCT differences.

Conclusions: Our results suggest that clinically meaningful differences are unlikely in OCT thickness or visual acuity following application of PRP in 1 sitting compared with 4 sittings in subjects in this cohort. More definitive results would require a large randomized trial.

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Gastroenterology

Gordon, S. C. and K. E. Sherman (2009). "Treatment of HBV/HCV coinfection: Releasing the enemy within." *Gastroenterology* **136**(2): 393-6. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, MI

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Hypertension & Vascular Research

Li, X. C. and J. L. Zhuo (2008). "In vivo regulation of AT1a receptor-mediated intracellular uptake of [125I]Val5-ANG II in the kidneys and adrenals of AT1a receptor-deficient mice." *Am J Physiol Renal Physiol* **294**(2): F293-302. PMC2277523. [PDF Full-Text](#)

Division of Hypertension and Vascular Research, Department of Internal Medicine, Henry Ford Hospital

Using type 1a angiotensin receptor (AT1a) receptor-deficient (Agtr1a^{-/-}) mice and in vivo autoradiography, we tested the hypothesis that intracellular uptake of ANG II in the kidney and adrenal glands is primarily mediated by AT1a receptors and that the response is regulated by prevailing endogenous ANG II. After pretreatment of wild-type (Agtr1a^{+/+}) and Agtr1a^{-/-} mice (n = 6-9 each group) with or without captopril (25 mg.kg⁻¹).day⁻¹) or losartan (10 mg.kg⁻¹).day⁻¹) for 2 wk, [125I]Val5-ANG II was infused for 60 min. Intracellular uptake of [125I]Val5-ANG II was determined by quantitative in vivo autoradiography after washout of circulating [125I]Val5-ANG II. Basal intracellular ANG II levels were 65% lower in the kidney (P < 0.001), but plasma ANG II levels were threefold higher, in Agtr1a^{-/-} than wild-type mice (P < 0.01). Although plasma [125I]Val5-ANG II levels were similar, urinary excretion of [125I]Val5-ANG II was fourfold higher in Agtr1a^{-/-} mice (P < 0.001). By contrast, intracellular [125I]Val5-ANG II levels were approximately 80% lower in the kidney and adrenal glands of Agtr1a^{-/-} mice (P < 0.01). Captopril decreased endogenous plasma and renal ANG II levels (P < 0.01) but increased intracellular uptake of [125I]Val5-ANG II in the kidney and adrenal glands of wild-type and Agtr1a^{-/-} mice (P < 0.01). Losartan largely blocked renal and adrenal uptake of [125I]Val5-ANG II in wild-type and Agtr1a^{-/-} mice. Thus 80% of intracellular ANG II uptake in the kidney and adrenal glands is mediated by AT1a receptors, whereas AT1b receptor- and other non-receptor-mediated mechanisms account for 20% of the response. Our results suggest that AT1a receptor-mediated uptake of extracellular ANG II may play a physiological role in the kidney and adrenal glands.

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Hypertension & Vascular Research

Liu, Y. H., M. D'Ambrosio, T. D. Liao, H. M. Peng, N. E. Rhaleb, U. Sharma, S. Andre, H. J. Gabius and O. A. Carretero (2009). "N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin." Am J Physiol Heart Circ Physiol **296**(2): H404-H412. [PDF Full-Text](#)

Henry Ford Hospital, Hypertension & Vascular Research Division, Department of Internal Medicine, Detroit, MI 48202

Galectin-3 (Gal-3) is secreted by activated macrophages. In hypertension, Gal-3 is a marker for hypertrophic hearts prone to develop heart failure. Gal-3 infused in pericardial sac leads to cardiac inflammation, remodeling, and dysfunction. N-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP), a naturally occurring tetrapeptide, prevents and reverses inflammation and collagen deposition in the heart in hypertension and heart failure postmyocardial infarction. In the present study, we hypothesize that Ac-SDKP prevents Gal-3-induced cardiac inflammation, remodeling, and dysfunction, and these effects are mediated by the transforming growth factor (TGF)-beta/Smad3 signaling pathway. Adult male rats were divided into four groups and received the following intrapericardial infusion for 4 wk: 1) vehicle (saline, n = 8); 2) Ac-SDKP (800 mu g.kg(-1).day(-1), n = 8); 3) Gal-3 (12 mu g/day, n = 7); and 4) Ac-SDKP + Gal-3 (n = 7). Left ventricular ejection fraction, cardiac output, and transmitral velocity were measured by echocardiography; inflammatory cell infiltration, cardiomyocyte hypertrophy, and collagen deposition in the heart by histological and immunohistochemical staining; and TGF-beta expression and Smad3 phosphorylation by Western blot. We found that, in the left ventricle, Gal-3 1) enhanced macrophage and mast cell infiltration, increased cardiac interstitial and perivascular fibrosis, and causes cardiac hypertrophy; 2) increased TGF-beta expression and Smad3 phosphorylation; and 3) decreased negative change in pressure over time response to isoproterenol challenge, ratio of early left ventricular filling phase to atrial contraction phase, and left ventricular ejection fraction. Ac-SDKP partially or completely prevented these effects. We conclude that Ac-SDKP prevents Gal-3-induced cardiac inflammation, fibrosis, hypertrophy, and dysfunction, possibly via inhibition of the TGF-beta/Smad3 signaling pathway.

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Hypertension & Vascular Research

Ren, Y. L., J. L. Garvin, R. S. Liu and O. A. Carretero (2009). "Cross-talk between arterioles and tubules in the kidney." Ped Nephrol **24**(1): 31-5. [PDF Full-Text](#)

Henry Ford Hospital, Division of Hypertension & Vascular Research, Detroit, MI

In hypertension the pressure natriuresis set point is shifted to a higher pressure due to an increase in both renal vascular resistance and sodium (Na) reabsorption. The afferent arterioles (Af-Arts) and efferent arterioles (Ef-Arts) account for most renal vascular resistance; they control glomerular filtration rate (GFR) and peritubular pressure, and, consequently, renal function. Af-Art and Ef-Art resistance is regulated by factors similar to those in other arterioles and also by tubuloglomerular feedback (TGF). TGF operates via the macula densa, which senses increases in sodium chloride (NaCl) and sends a signal that constricts the Af-Art and dilates the Ef-Art. In the outer renal cortex, the connecting tubule (CNT) returns to the glomerular hilus and contacts the Af-Art. This morphology is compatible with cross-talk between the CNT and Af-Art, so-called connecting tubule glomerular feedback (CTGF). Our studies show that increasing NaCl delivery to the CNT results in Af-Art dilatation that can be blocked by inhibitors of Na transport. We believe cross-talk between the CNT and Af-Art is a novel mechanism that may contribute to regulation of renal blood flow and GFR.

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Hypertension & Vascular Research

Xu, J., O. A. Carretero, E. G. Shesely, N. E. Rhaleb, J. J. Yang, M. Bader and X. P. Yang (2009). "The kinin B-1 receptor contributes to the cardioprotective effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in mice." Exp Physiol **94**(3): 322-9. [PDF Full-Text](#)

Henry Ford Hospital, Department of Internal Medicine, Hypertension & Vascular Research Division, Detroit, MI 48202

Recent studies have shown that inhibition of angiotensin-converting enzyme (ACE) or angiotensin II receptors causes upregulation of the B-1 receptor (B1R). Here we tested the hypothesis that activation of the B1R partly contributes to the cardiac beneficial effect of ACE inhibitor (ACEi) and angiotensin II receptor blockers (ARB). B1R knockout mice (B1R^{-/-}) and C57Bl/6J (wild-type control animals, WT) were subjected to myocardial infarction (MI) by ligating the left anterior descending coronary artery. Three weeks after MI, each strain of mice was treated with vehicle, ACEi (ramipril, 2.5 mg kg⁻¹ day⁻¹) in drinking water or ARB (valsartan, 40 mg kg⁻¹ day⁻¹) in drinking water for 5 weeks. We found that: (1) compared with WT mice, B1R^{-/-} mice that underwent sham surgery had slightly but significantly increased left ventricular (LV) diastolic dimension, LV mass and myocyte size, whereas systolic blood pressure, cardiac function and collagen deposition did not differ between strains; (2) MI leads to LV hypertrophy, chamber dilatation and dysfunction similarly in both WT and B1R^{-/-} mice; and (3) ACEi and ARB improved cardiac function and remodelling in both strains; however, these benefits were significantly diminished in B1R^{-/-} mice. Our data suggest that kinins, acting via the B1R, participate in the cardioprotective effects of ACEi and ARB.

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Internal Medicine

Hobbs, R. D., Z. Habib, D. Alromaihi, L. Idi, N. Parikh, F. Blocki and D. S. Rao (2009). "Severe vitamin D deficiency in Arab-American women living in Dearborn, Michigan." Endocr Pract **15**(1): 35-40. [Article Request Form](#)

Henry Ford Hospital, Detroit, Michigan 48202, USA. rhobbs1@hfhs.org

OBJECTIVE: To determine the prevalence and degree of 25-hydroxyvitamin D deficiency in a group of Arab-American women in the largest, most-concentrated Arab-American settlement in the United States and to search for correlations with dress, diet, and use of vitamin D-fortified foods and vitamin supplements.

METHODS: In this cross-sectional study, Arab-American women, 18 years and older, who attended an ethnic market on April 7 or 14, 2007, were recruited. Participants were interviewed by bilingual English- and Arabic-speaking investigators using a semi-structured interview to assess dress; demographic variables; medical history; medication use; clinical symptoms associated with vitamin D deficiency (eg, joint or bone pain, muscle weakness); and dietary intake of vitamin D from fortified orange juice, milk, and vitamin supplementation. Blood samples were drawn to measure concentrations of serum calcium, creatinine, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D. Participants were initially divided into 2 groups based on whether the woman was veiled and further subdivided into 3 groups on the basis of vitamin D intake from supplemented food sources (milk or vitamin D-fortified orange juice) and vitamin pills: unveiled, veiled and taking supplements, and veiled and taking no supplements.

RESULTS: Eighty-seven women participated. Serum 25-hydroxyvitamin D levels were uniformly low, with the highest levels in the unveiled group (median [interquartile range]) (8.5 ng/mL [5.75-13.5 ng/mL]) followed by the veiled, supplemented group (7 ng/mL [4-11.5 ng/mL]) and the veiled, unsupplemented group (4 ng/mL [2-6.8 ng/mL]). 25-Hydroxyvitamin D levels were lower in women with less experience in the United States and in those with less education. Vitamin D-fortified orange juice consumption had a greater positive predictive effect on serum 25-hydroxyvitamin D levels than either milk or vitamin pills and may possibly serve as a surrogate marker for vitamin D awareness.

CONCLUSIONS: Vitamin D deficiency, as assessed by 25-hydroxyvitamin D concentrations, is endemic in a sample of Arab-American women living in Dearborn, Michigan. These findings potentially identify an important health problem in the largest, most-concentrated Arab-American population in the United States.

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Medical Genetics

Moosavi, S. A., J. Sanchez and A. Adeyinka (2009). "Marker chromosomes are a significant mechanism of high-level RUNX1 gene amplification in hematologic malignancies." Cancer Genet Cytogenet **189**(1): 24-8. [Article Request Form](#)

Henry Ford Hospital, Department of Medical Genetics, Detroit, MI 48202

To understand the cytogenetic mechanisms responsible for multiple RUNX1 gene copy numbers in hematologic malignancies, we analyzed the chromosomal and molecular cytogenetic findings in bone marrow or peripheral blood samples of individuals who were diagnosed with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or acute lymphoblastic leukemia (ALL). Included in the analysis were 113 consecutive samples received in our laboratory between January 2005 and June 2007. Bone marrow and/or peripheral blood samples were characterized using conventional G-banding techniques and fluorescent in situ

hybridization (FISH) techniques with commercially available RUNX1/RUNX1T1 or ETV6/RUNX1 dual-color fusion probes. Eighty-one (72%) of the 113 samples showed an abnormal karyotype and/or abnormal FISH results. Eight of these had, by interphase FISH, RUNX1/RUNX1T1 or RUNX1/ETV6 fusion, and 19 had three or more RUNX1 signals not related to fusion with RUNX1T1 or ETV6 gene. Of the 19 cases with multiple RUNX1 gene signals, 5 had high-level RUNX1 amplification - defined as 5 or more RUNX1 signals in interphase cells - whereas the remaining 14 had 3-4 RUNX1 signals. Four of the five tumors with high-level RUNX1 amplification were myeloid disorders - three cases of AML and one case of MDS. The karyotypes of tumors with high-level amplification of RUNX1 were significantly characterized by the presence of marker chromosomes that harbored extra copies of the RUNX1 gene compared with tumors that had three to four RUNX1 gene signals ($P = 0.026$, Fisher's exact test). Our findings show that high-level RUNX1 amplification, especially in myeloid disorders, often results from marker chromosomes harboring extra copies of the RUNX1 gene. This suggests that amplification of RUNX1 in these tumors may be secondary to a previous rearrangement of 21q22, which later evolved into a complex marker chromosome as part of tumor progression.

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Neurology

Bowyer, S. M., L. Hsieh, J. E. Moran, R. A. Young, A. Manoharan, C. C. J. Liao, K. Malladi, Y. J. Yu, Y. R. Chiang and N. Tepley (2009). "Conversation effects on neural mechanisms underlying reaction time to visual events while viewing a driving scene using MEG." Brain Res **1251**: 151-61. [PDF Full-Text](#)

Henry Ford Hospital, Department of Neurology, MEG Lab, Detroit, MI 48202

Magnetoencephalography (MEG) imaging examined the neural mechanisms that modulate reaction times to visual events while viewing a driving video, with and without a conversation. Twenty-four subjects ages 18-65 were monitored by whole-head MEG. The primary tasks were to monitor a driving video and to depress a foot pedal in response to a small red light presented to the left or below the driving scene at unpredictable times. The behavioral reaction time (AT) to the lights was recorded. The secondary task was a hands-free conversation. The subject pressed a button to answer a ring tone, and then covertly answered pre-recorded non-emotional questions such as "What is your birth date?" RTs for the conversation task (1043 ms, SE=65 ms) were slightly longer than for the primary task (baseline no conversation (944 ms, SE=48 ms)). During the primary task RTs were inversely related to the amount of brain activity detected by MEG in the right superior parietal lobe (Brodmann's Area 7). Brain activity was seen in the 200 to 300 ms range after the onset of the red light and in the visual cortex (BA 19) about 85 ms after the red light. Conversation reduced the strengths of these regression relationships and increased mean RT. Conversation may contribute to increased reaction times by (1) damping brain activation in specific regions during specific time windows, or (2) reducing facilitation from attention inputs into those areas or (3) increasing temporal variability of the neural response to visual events. These laboratory findings should not be interpreted as indicative of real-world driving, without on-road validation, and comparison to other in-vehicle tasks.

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Neurology

Chen, J., X. Cui, A. Zacharek, G. L. Ding, A. Shehadah, Q. Jiang, M. Lu and M. Chopp (2009). "Niaspan treatment increases tumor necrosis factor-alpha-converting enzyme and promotes arteriogenesis after stroke." J Cereb Blood Flow Metab. Epub Ahead of Print. [Article Request Form](#)

Department of Neurology, Henry Ford Health Sciences Center, Detroit, Michigan, USA.

We tested the hypothesis that Niaspan (a prolonged release formulation of niacin) increases tumor necrosis factor-alpha-converting enzyme (TACE) expression and Notch signaling activity and promotes arteriogenesis after stroke. Rats were subjected to middle cerebral artery occlusion and were treated with or without Niaspan. Niaspan significantly elevated local cerebral blood flow, and increased arteriogenesis as indicated by increased arterial diameter and vascular smooth muscle cell (VSMC) proliferation in the ischemic brain after stroke. The increased arteriogenesis significantly correlated with the functional outcome after stroke. Niaspan treatment of stroke upregulated TACE, Notch1, and Notch intracellular domain expression in the ischemic brain. To further investigate the mechanisms of Niaspan-induced arteriogenesis, a primary brain arterial culture was used. Niacin treatment significantly increased arterial sprouting and VSMC migration compared with

control nontreated arterial cells. Inhibition of TACE by the TACE inhibitor or knockdown of TACE gene expression in brain arterial culture significantly attenuated Niacin-induced arterial sprouting and VSMC migration. In addition, TACE treatment of arterial culture significantly increased arterial VSMC migration and arterial sprouting. Knockdown of Notch1 marginally decreased arterial sprouting and VSMC migration compared with scrambled control. Niaspan promotes arteriogenesis, which is mediated, in part, by TACE.

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Neurology

Cui, X., J. L. Chen, A. Zacharek, C. Roberts, Y. P. Yang and M. Chopp (2009). "Nitric oxide donor up-regulation of SDF1/CXCR4 and Ang1/Tie2 promotes neuroblast cell migration after stroke." *J Neurosci Res* **87**(1): 86-95. [PDF Full-Text](#)

Henry Ford Health System, Department of Neurology, Detroit, MI

We tested the hypothesis that a nitric oxide donor, DETA-NONOate, up-regulates stromal cell-derived factor-1 (SDF1) and angiopoietin 1 (Ang1) in the ischemic brain and their respective receptors chemokine CXC motif receptor 4 (CXCR4) and Tie2 in the subventricular zone (SVZ) and thereby promote SVZ neuroblast cell migration after stroke. C57BL/6J mice were subjected to middle cerebral artery occlusion (MCAo), and 24 hr later DETA-NONOate (0.4 mg/kg) or phosphate-buffered solution was intravenously administered. Mice were sacrificed at 14 days for histological assessment or sacrificed at 3 days for analysis by real-time polymerase chain reaction and migration after MCAo. To elucidate whether SDF1/CXCR4 and Ang1/Tie2 pathways mediate DETA-NONOate-induced SVZ migration after stroke, SDF1 alpha, Ang1 peptide, a specific antagonist of CXCR4 (AMD3100), and a neutralizing antibody of Tie2 (anti-Tie2) were used in vitro. DETA-NONOate significantly increased the percentage area of doublecortin (DCX, a marker of migrating neuroblasts)-immunoreactive cells in the SVZ and ischemic boundary zone. DETA-NONOate significantly increased the expression of SDF1 and Ang1 in the ischemic border and up-regulated CXCR4 and Tie2 in the SVZ compared with MCAo control. DCX-positive cell migration from SVZ explants was significantly increased in the DETA-NONOate treatment group compared with MCAo-alone animals. In vitro, SDF1 alpha and Ang1 significantly increased SVZ explants cell migration. In addition, inhibition of CXCR4 or Tie2 significantly attenuated DETA-NONOate-induced SVZ cell migration. Our data indicate that treatment of stroke with a nitric oxide donor up-regulates SDF1/CXCR4 and Ang1/Tie2 pathways and thereby likely increases SVZ neuroblast cell migration.

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Neurology

Hsieh, L., R. A. Young, S. M. Bowyer, J. E. Moran, R. J. Genik, C. C. Green, Y. R. Chiang, Y. J. Yu, C. C. Liao and S. Seaman (2009). "Conversation effects on neural mechanisms underlying reaction time to visual events while viewing a driving scene: fMRI analysis and asynchrony model." *Brain Res* **1251**: 162-75. [PDF Full-Text](#)

Henry Ford Hospital, Department of Neurology, MEG Lab, Detroit, MI 48202

Magnetoencephalography (MEG) imaging examined the neural mechanisms that modulate reaction times to visual events while viewing a driving video, with and without a conversation. Twenty-four subjects ages 18-65 were monitored by whole-head MEG. The primary tasks were to monitor a driving video and to depress a foot pedal in response to a small red light presented to the left or below the driving scene at unpredictable times. The behavioral reaction time (AT) to the lights was recorded. The secondary task was a hands-free conversation. The subject pressed a button to answer a ring tone, and then covertly answered pre-recorded non-emotional questions such as "What is your birth date?" RTs for the conversation task (1043 ms, SE=65 ms) were slightly longer than for the primary task (baseline no conversation (944 ms, SE=48 ms)). During the primary task RTs were inversely related to the amount of brain activity detected by MEG in the right superior parietal lobe (Brodmann's Area 7). Brain activity was seen in the 200 to 300 ms range after the onset of the red light and in the visual cortex (BA 19) about 85 ms after the red light. Conversation reduced the strengths of these regression relationships and increased mean RT. Conversation may contribute to increased reaction times by (1) damping brain activation in specific regions during specific time windows, or (2) reducing facilitation from attention inputs into those areas or (3) increasing temporal variability of the neural response to visual events. These laboratory findings should not be interpreted as indicative of real-world driving, without on-road validation, and comparison to other in-vehicle tasks.

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Neurology

Katramados, A. M., D. Burdette, S. C. Patel, L. R. Schultz, S. Gaddam and P. D. Mitsias (2009). "Periictal diffusion abnormalities of the thalamus in partial status epilepticus." *Epilepsia* **50**(2): 265-75. [PDF Full-Text](#)

Henry Ford Health Science Center, Department of Neurology, Detroit, MI

To identify and describe thalamic dysfunction in patients with temporal as well as extratemporal status epilepticus (SE) and to also analyze the specific clinical, radiological, and electroencephalography (EEG) characteristics of patients with acute thalamic involvement.

We retrospectively identified patients who presented with clinical and electrographic evidence of partial SE and had thalamic abnormalities on diffusion-weighted imaging (DWI) within 5 days of documentation of lateralized epileptiform discharges (group 1). The spatial and temporal characteristics of the periodic lateralized epileptiform discharges (PLEDs) and the recorded electrographic seizures were analyzed and correlated with magnetic resonance imaging (MRI)-DWI hyperintense lesions. The findings of group 1 patients were compared with those of patients with partial SE without thalamic abnormalities on DWI (group 2).

The two groups were similar with regard to clinical presentation and morphology of epileptiform discharges. Group 1 patients had thalamic hyperintense lesions on DWI that appeared in the region of the pulvinar nucleus, ipsilateral to the epileptiform activity. Statistically significant relationship was noted between the presence of thalamic lesions and ipsilateral cortical laminar involvement ($p = 0.039$) as well as seizure origin in the posterior quadrants ($p = 0.038$). A trend towards PLEDs originating in the posterior quadrants was also noted ($p = 0.077$).

Thalamic DWI hyperintense lesions may be observed after prolonged partial SE and are likely the result of excessive activity in thalamic nuclei having reciprocal connections with the involved cortex. The thalamus likely participates in the evolution and propagation of partial seizures in SE.

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Neurology

Liu, X. S., M. Chopp, X. G. Zhang, R. L. Zhang, B. Buller, A. Hozeska-Solgot, S. R. Gregg and Z. G. Zhang (2009). "Gene profiles and electrophysiology of doublecortin-expressing cells in the subventricular zone after ischemic stroke." *J Cereb Blood Flow Metab* **29**(2): 297-307. [Article Request Form](#)

Henry Ford Hospital, Department of Neurology, Detroit, MI

Stroke increases neuroblasts in the subventricular zone (SVZ) of the lateral ventricle and these neuroblasts migrate toward the ischemic boundary to replace damaged neurons. Using brain slices from the nonischemic adult rat and transgenic mice that expressed enhanced green fluorescent protein (EGFP) concomitantly with doublecortin (DCX), a marker for migrating neuroblasts, we recorded electrophysiological characteristics while simultaneously analyzing the gene expression in single SVZ cells. We found that SVZ cells expressing the DCX gene from the nonischemic rat had a mean resting membrane potential (RMP) of -30mV . DCX-EGFP-positive cells in the nonischemic SVZ of the transgenic mouse had a mean RMP of $-25 \pm 7\text{ mV}$ and did not exhibit Na^+ currents, characteristic of immature neurons. However, DCX-EGFP-positive cells in the ischemic SVZ exhibited a hyperpolarized mean RMP of $-54 \pm 18\text{ mV}$ and displayed Na^+ currents, indicative of more mature neurons. Single-cell multiplex RT-PCR analysis revealed that DCX-EGFP-positive cells in the nonischemic SVZ of the transgenic mouse expressed high neural progenitor marker genes, Sox2 and nestin, but not mature neuronal marker genes. In contrast, DCX-EGFP-positive cells in the ischemic SVZ expressed tyrosine hydroxylase, a mature neuronal marker gene. Together, these data indicate that stroke changes gene profiles and the electrophysiology of migrating neuroblasts.

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Neurology

Russman, A. N., L. R. Schultz, I. F. Zaman, M. F. Rehman, B. Silver, P. Mitsias and D. R. Nerenz (2009). "A significant temporal and quantitative relationship exists between high-

density lipoprotein levels and acute ischemic stroke presentation." *J Neurol Sci* **279**(1-2): 53-6. [PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA; Neuroscience Institute, Henry Ford Hospital, Detroit, Michigan, USA.

BACKGROUND: Reduced serum high-density lipoprotein (HDL-C) is an independent risk factor for ischemic stroke in elderly men. The temporal and quantitative relationships between HDL-C and acute ischemic stroke have not been defined. **METHODS:** We identified patients with first ever acute ischemic stroke presenting to our hospital between 2003 and 2006. Patients with serum fasting lipid levels drawn within 24 h of admission and at least one follow-up visit with a neurologist in our hospital were included. Clinical and laboratory data before, immediately after, and several weeks after the index stroke were collected. **RESULTS:** 191 patients were included (47% women, mean age 62 years). The mean time interval between pre-stroke lipid data and index stroke was 5.2 months; 50% of these patients were taking a statin medication. The mean time interval between index stroke and follow-up lipid testing was 2.6 months. Immediately after the index stroke, HDL-C levels decreased by 18% ($p < 0.001$) relative to pre-stroke levels. This phenomenon was independent of stroke severity, and was blunted among patients with a prior history of myocardial infarction ($p < 0.01$). HDL-C levels increased to pre-stroke levels within 3 months post-stroke. **CONCLUSIONS:** HDL-C levels decrease significantly at the time of acute ischemic stroke. Prior history of myocardial infarction diminishes HDL-C depression at the time of stroke. HDL-C may be an acute phase reactant or nascent biomarker of acute stroke susceptibility. Further prospective studies are needed.

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Neurology

Schuh, L. A., J. C. Adair, O. Drogan, B. M. Kissela, J. C. Morgenlander and J. R. Corboy (2009). "Education research: neurology residency training in the new millennium." *Neurology* **72**(4): e15-20. [PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital, Detroit, MI 48202, USA.

lschuh@neuro.hfh.edu

OBJECTIVE: To survey adult neurology program directors (ANPD) to identify their most pressing needs at a time of dramatic change in neurology resident education. **METHODS:** All US ANPD were surveyed in 2007 using an instrument adjusted from a 1999 survey instrument. The goal was to characterize current program content, the institution and evaluation of the core competencies, program director characteristics, program director support, the institution of work duty hour requirements, resident support, and the curriculum needs of program directors and programs. **RESULTS:** A response rate of 82.9% was obtained. There is a significant disconnect between administration time spent by ANPD and departmental/institutional support of this, with ANPD spending approximately 35% of a 50-hour week on administration with only 16.7% salary support. Rearrangement of rotations or services has been the most common mode for ANPD to deal with work duty hour requirements, with few programs employing mid level providers. Most ANPD do not feel work duty hour reform has improved resident education. More residents are entering fellowships following graduation than documented in the past. Curriculum deficiencies still exist for ANPD to meet all Neurology Program Requirements, especially for nontraditional neurology topics outside the conventional bounds of clinical neurology (e.g., practice management). Nearly one quarter of neurology residency programs do not have a meeting or book fund for every resident in the program. **CONCLUSIONS:** Adult neurology program directors (ANPDs) face multiple important financial and organizational hurdles. At a time of increasing complexity in medical education, ANPDs need more institutional support.

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Neurology

Zhang, J., C. Brodie, Y. Li, X. Zheng, C. Roberts, M. Lu, Q. Gao, J. Borneman, S. Savant-Bhonsale, S. B. Elias and M. Chopp (2009). "Bone marrow stromal cell therapy reduces proNGF and p75 expression in mice with experimental autoimmune encephalomyelitis." *J Neurol Sci* **279**(1-2): 30-8. [PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Detroit, MI, 48202, USA.

Demyelination is prominent in experimental autoimmune encephalomyelitis (EAE). The receptor p75 and its high affinity ligand proNGF are required for oligodendrocyte death after injury. We hypothesize that bone marrow stromal cells (BMSCs) provide therapeutic benefit in EAE mice by reducing proNGF/p75 expression. PBS or BMSCs (2×10^6) were administered intravenously on the day of EAE onset. Neurological function and demyelination areas were measured. Immunohistochemical staining was used to measure apoptotic oligodendrocytes, expression of proNGF and p75, and the relationship between proNGF and p75 in neural cells. proNGF was used to treat oligodendrocytes in culture with or without BMSCs. EAE mice exhibited neurological function deficit and demyelination, and expression of proNGF and p75 was increased. BMSC treatment improved functional recovery, reduced demyelination area and apoptotic oligodendrocytes, decreased expression of proNGF and p75 compared with PBS treatment. proNGF(+) cells colocalized with neural cell markers, while p75 colocalized with an oligodendrocytic marker, and proNGF colocalized with p75. proNGF induced apoptosis of oligodendrocytes in vitro, and p75 antibody blocked this apoptotic activity. BMSCs reduced p75 expression and apoptotic activity in oligodendrocytes with proNGF treatment. BMSC treatment benefits on EAE mice may be fostered by decreasing the cellular expression of proNGF and p75, thereby reducing oligodendrocyte death.

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Neurosurgery

Hong, X., F. Jiang, S. N. Kalkanis, Z. G. Zhang, X. Zhang, X. Zheng, H. Jiang and M. Chopp (2009). "Intracellular free calcium mediates glioma cell detachment and cytotoxicity after photodynamic therapy." *Lasers Med Sci*. EPub Ahead of Print. [PDF Full-Text](#)

Department of Neurosurgery, Henry Ford Hospital, Detroit, MI, USA.

Photofrin photodynamic therapy (PDT) caused a dose-dependent decrease of enzymatic cell detachment by trypsin/ethylenediamine tetra-acetic acid (EDTA) in human glioma U251n and U87 cells. This happened coincidentally with the increase of intracellular free calcium ($[Ca^{2+}]_i$). Thapsigargin, which increased $[Ca^{2+}]_i$, induced further decrease in enzymatic cell detachment and increased cytotoxicity. Opposite effects were observed when 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetra-acetic acid tetrakis, an intracellular Ca^{2+} chelator, was used. PDT-induced changes in $[Ca^{2+}]_i$ and cell detachment were not blocked by calcium channel antagonists nickel (Ni^{2+}) or nimodipine, nor were they altered when cells were irradiated in a buffer free from Ca^{2+} and magnesium (Mg^{2+}), suggesting that $[Ca^{2+}]_i$ is derived from the internal calcium stores. Decreased cell migration was observed after PDT, as assessed by chemotactic and wound-healing assays. Our findings indicated that internal calcium store-derived $[Ca^{2+}]_i$ plays an important role in PDT-induced enzymatic cell detachment decrease and cytotoxicity. Cell migration may be affected by these changes.

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Neurosurgery

Mahmood, A., A. Goussev, D. Y. Lu, C. S. Qu, Y. K. Xiong, H. and M. Chopp (2008). "Long-lasting benefits after treatment of traumatic brain injury (TBI) in rats with combination therapy of marrow stromal cells (MSCs) and simvastatin." *J Neurotrauma* **25**(12): 1441-7.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Health System, Department of Neurosurgery, Detroit, MI

This study was designed to investigate the beneficial effects of combination therapy of simvastatin and marrow stromal cells (MSCs) in improving functional outcome after traumatic brain injury (TBI) in rats. Adult female Wistar rats ($n = 72$ and 8 , per group) were injured with controlled cortical impact and treated either with monotherapy of MSCs or simvastatin or a combination therapy of these two agents. Different combination doses were tested, and nine groups of animals were studied. Neurological function was evaluated using Modified Neurological Severity Score (MNSS), and animals were sacrificed 3 months after injury. Coronal brain sections were stained with standard hematoxylin and eosin immunohistochemistry. Our results showed that, though functional improvement was seen with monotherapies of MSCs and simvastatin, the combination

therapy when used in optimal doses was significantly better in improving functional outcome. This improvement was long lasting and persisted until the end of the trial (3 months). The optimum combination dose was 0.5mg of simvastatin combined with 2×10^6 MSCs. post mortem analysis showed the presence of donor MSCs within the injured cortex. Endogenous cellular proliferation induced by the neurorestorative treatments was also observed in the lesion boundary zone. Our data show that MSCs and simvastatin have a synergistic effect in improving functional outcome after TBI.

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Neurosurgery

Martino, M. M., M. Mochizuki, D. A. Rothenfluh, S. A. Rempel, J. A. Hubbell and T. H. Barker (2009). "Controlling integrin specificity and stem cell differentiation in 2D and 3D environments through regulation of fibronectin domain stability." *Biomaterials* **30**(6): 1089-97. [Article Request Form](#)

Henry Ford Hospital, Department of Neurosurgery, Barbara Jane Levy Lab Molecular Neurooncology, Hermelin Brain Tumor Center, Detroit, MI 48202

The extracellular matrix (ECM) exerts powerful control over many cellular phenomena, including stem cell differentiation. As such, design and modulation of ECM analogs to ligate specific integrin is a promising approach to control cellular processes *in vitro* and *in vivo* for regenerative medicine strategies. Although fibronectin (FN), a crucial ECM protein in tissue development and repair, and its RGD peptide are widely used for cell adhesion. the promiscuity with which they engage integrins leads to difficulty in control of receptor-specific interactions. Recent simulations of force-mediated unfolding of FN domains all sequences analysis of human versus mouse FN suggest that the structural stability of the FN's central cell-binding domains (FN 1119-10) affects its integrin specificity. Through production of FN 1119-10 variants with variable stabilities, we obtained ligands that present different specificities for the integrin $\alpha(5)\beta(1)$ and that can be covalently linked into fibrin matrices. Here, we demonstrate the capacity of 9513, integrin-specific engagement to influence human mesenchymal stem cell (MSC) behavior in 2D and 3D environments. Our data indicate that $\alpha(5)\beta(1)$, has an important role in the control of MSC osteogenic differentiation. FN fragments with increased specificity for $\alpha(5)\beta(1)$ versus $\alpha(v)\beta(3)$ results in significantly enhanced osteogenic differentiation of MSCs in 2D and in a clinically relevant 3D fibrin matrix system, although attachment/spreading and proliferation were comparable with that on full-length FN. This work shows how integrin-dependant cellular interactions with the ECM can be engineered to control stem cell fate, within a system appropriate for both 3D cell Culture and tissue engineering.

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Neurosurgery

Mikkelsen, T., C. Brodie, S. Finniss, M. E. Berens, J. L. Rennert, K. Nelson, N. Lemke, S. L. Brown, D. Hahn, B. Neuteboom and S. L. Goodman (2008). "Radiation sensitization of glioblastoma by cilengitide has unanticipated schedule-dependency." *Int J Cancer*. Epub Ahead of Print. [PDF Full-Text](#)

Department of Neurosurgery, Hermelin Brain Tumor Center, Henry Ford Hospital, Detroit, MI.

We investigated whether cilengitide could amplify the antitumor effects of radiotherapy in an orthotopic rat glioma xenograft model. Cilengitide is a specific inhibitor of αv series integrins, and acts as an antiangiogenic. U251 human glioma cells express $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins. We used *in vitro* assays of adhesion and growth of tumor and endothelial cells to evaluate cytotoxicity and the potential for cilengitide to enhance radiation toxicity. Treatment was then evaluated in an orthotopic model to evaluate synergy with therapeutic radiation *in vivo*. *In vitro*, cilengitide blocked cell adhesion, but did not influence the effects of radiation on U251 cells; cilengitide strongly amplified radiation effects on endothelial cell survival. *In vivo*, radiotherapy prolonged the survival of U251 tumor-bearing rats from 50 to over 110 days. Cotreatment with cilengitide and radiation dramatically amplified the effects of radiation, producing survival over 200 days and triggering an enhanced apoptotic response and suppression of tumor growth by histology at necropsy. Signaling pathways activated in the tumor included NF κ B, a documented mediator of cellular response to radiation. Because cilengitide has a short plasma half-life ($t_{1/2}$) approximately 20 min), antiangiogenic scheduling typically uses daily injections. We found that a single dose of cilengitide (4 mg/kg) given between 4

and 12 hr prior to radiation was sufficient to produce the same effect. Our results demonstrate that blockade of alphav integrins mediates an unanticipated rapid potentiation of radiation, and suggests possible clinical translation for glioma therapy.

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Neurosurgery

Mikkelsen, T., T. Doyle, J. Anderson, J. Margolis, N. Paleologos, J. Gutierrez, D. Croteau, L. Hasselbach, R. Avedissian and L. Schultz (2009). "Temozolomide single-agent chemotherapy for newly diagnosed anaplastic oligodendroglioma." J Neurooncol **92**(1): 57-63. [PDF Full-Text](#)

Hermelin Brain Tumor Center, Henry Ford Health System, 2799 W Grand Blvd, Detroit, MI, 48202, USA, nstom@neuro.hfh.edu.

The treatment of patients with anaplastic oligodendroglioma (AO) has been significantly impacted by the molecular detection of loss of sequences on chromosomes 1p and 19q. We performed a clinical trial to prospectively evaluate the safety of treating patients with AO with temozolomide (TMZ) alone in patients with chromosome 1p/19q loss and with chemo-radiation in patients not harboring this loss. Forty-eight patients were enrolled, 36/48 (75%) with evidence of chromosome 1p/19q loss treated with TMZ alone and 12/18 (25%) without such losses, treated with pre-radiation TMZ followed by chemo-radiation. Despite more aggressive treatment, patients without 1p/19q loss had a shorter progression-free survival (PFS) of 13.5 months. With a median follow-up time of 32 months, patients with 1p/19q LOH had a median TTP of 28.7 months. Patients with AO with 1p/19q LOH can be safely treated with single-agent TMZ and do not appear to experience earlier or more frequent tumor progression. This treatment regimen should be studied as part of a formal randomized clinical trial.

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Neurosurgery

Torcuator, R., R. Zuniga, Y. S. Mohan, J. Rock, T. Doyle, J. Anderson, J. Gutierrez, S. Ryu, R. Jain, M. Rosenblum and T. Mikkelsen (2009). "Initial experience with bevacizumab treatment for biopsy confirmed cerebral radiation necrosis." J Neurooncol. EPub Ahead of Print. [PDF Full-Text](#)

Hermelin Brain Tumor Center, Department of Neurosurgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI, 48202, USA, nsroy@neuro.hfh.edu.

Background Cerebral radiation necrosis is a serious complication of radiation treatment for brain tumors. Therapeutic options include corticosteroids, anticoagulation and hyperbaric oxygen with limited efficacy. Bevacizumab, an antibody against VEGF had been reported to reduce edema in patients with suspected radiation necrosis. We retrospectively reviewed 6 patients with biopsy proven cerebral radiation necrosis treated with bevacizumab between 2006 and 2008. Results Interval MRI follow-up demonstrated radiographic response in all patients with an average reduction of 79% for the post gadolinium studies and 49% for the FLAIR images. The initial partial radiographic response was noted for up to a mean follow-up time of 5.9 months (6 weeks to 18 months). Conclusion Bevacizumab appears to produce radiographic response and clinical benefits in the treatment of patients with cerebral radionecrosis.

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Neurosurgery

Zuniga, R. M., R. Torcuator, R. Jain, J. Anderson, T. Doyle, S. Ellika, L. Schultz and T. Mikkelsen (2009). "Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan." J Neurooncol **91**(3): 329-36. [PDF Full-Text](#)

Henry Ford Health System, Department of Neurosurgery, Detroit, MI 48202

Our objective is to assess treatment efficacy, safety and pattern of response and recurrence in patients with recurrent high-grade glioma treated with bevacizumab and irinotecan. We reviewed retrospectively 51 patients with recurrent high-grade glioma treated with this combination at the Henry Ford Hermelin Brain Tumor Center from 11/15/2005 to 04/01/2008. The 6-month progression-free survival (PFS) for anaplastic gliomas (AGs) was 78.6 and 63.7% for glioblastoma. The median PFS was 13.4 months for AG and 7.6 months for those with glioblastoma. The overall survival rate (OS) at 6 months was 85.7% for AG and 78.0% for glioblastoma. The 12-month OS was 77.9% for AG and 42.6% for glioblastoma. The median OS time for AGs was not reached and was 11.5 months for those with glioblastoma. Thirty-six out of 51 (70.59%) patients demonstrated partial (32/51) or complete (4/51) radiographic response to treatment and 8/51 (15.69%) remained stable. Of the 38 who demonstrated progression on post-gadolinium studies, 23 showed distant progression with or without local recurrence. Seven patients showed progression on FLAIR without concordant findings on post-Gd sequences. Six patients (11.76%) discontinued treatment due to a treatment-emergent adverse event, including one with end-stage renal failure and another with gastric perforation. No symptomatic intracranial hemorrhages were reported. Patients with recurrent high-grade glioma treated with bevacizumab plus irinotecan demonstrate an excellent radiographic response rate and improved clinical outcome when compared to historical data. The high rate of distant tumor progression suggests that tumors may adapt to inhibition of angiogenesis by increased infiltration and vascular co-option.

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Obstetrics & Gynecology

Bandyopadhyay, S., A. Sood, A. R. Munkarah, M. H. Arabi, H. Guan, K. Hayek and R. Ali-Fehmi (2009). "Role of EZH2 in ovarian carcinogenesis." Mod Pathol **22**(Suppl 1): 207A. [PDF Full-Text](#) - Scroll down to page 207A

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Otolaryngology

Seidman, M. D., W. Tang, N. Shirwany, U. Bai, C. J. Rubin, J. P. Henig and W. S. Quirk (2009). "Anti-intercellular adhesion molecule-1 antibody's effect on noise damage." Laryngoscope. Epub Ahead of Print. [PDF Full-Text](#)

Department of Otolaryngology, Henry Ford Health System, Detroit, Michigan, U.S.A.

OBJECTIVES/HYPOTHESIS:: The purpose of this study was to investigate possible preventive effects of anti-intercellular adhesion molecule-1 antibody (anti-ICAM-1 Ab) on noise-induced cochlear damage as assessed by changes in auditory thresholds and cochlear blood flow. **STUDY DESIGN::** A controlled animal study. Pretreated rats with anti-ICAM-1 Ab or saline control, followed with exposure to 72 continuous hours of broad band noise (107 dB SPL), and 24 hours after noise exposure treated again with anti-ICAM-1 Ab or saline. **METHODS::** Eighteen healthy male Fischer rats (200-250 g) were used. Sixteen were randomly selected to study noise-induced temporary threshold shifts. The remaining two rats were used to study cochlear blood flow (CBF), using laser Doppler flowmetry and blood pressure measurements. **RESULTS::** Rats treated with anti-ICAM-1 Ab (1.875 mg/kg, intravenously) showed attenuated temporary threshold shifts (TTS) compared to controls. Both groups showed a partial threshold recovery 72 hours following noise exposure, normal for this noise exposure paradigm. Comparisons of baseline and post-treatment measurements of CBF and mean arterial blood pressure revealed no significant changes. Anti-ICAM-1 Ab animals displayed significantly lower mean auditory threshold shifts at all five test frequencies ($P < .05$) when compared to control. **CONCLUSIONS::** Blocking the cascade of reactive oxygen species (ROS) generation by using anti-ICAM-Ab protects against noise-induced hearing loss.

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Pathology

Blouse, G. E., D. M. Dupont, C. R. Schar, J. K. Jensen, K. H. Minor, J. Y. Anagli, H. Gardsvoll, M. Ploug, C. B. Peterson and P. A. Andreasen (2009). "Interactions of Plasminogen Activator Inhibitor-1 with Vitronectin Involve an Extensive Binding Surface and Induce Mutual Conformational Rearrangements." Biochemistry. Epub Ahead of Print. [Article Request Form](#)

Laboratory of Cellular Protein Science, Department of Molecular Biology, University of Aarhus, Gustav Wieds Vej 10C, DK-8000 Aarhus C, Denmark, Department of Biochemistry, Cellular, and Molecular Biology and Center of Excellence in Structural Biology, University of Tennessee, Knoxville, Tennessee 37996, Finsen Laboratory 3735, Rigshospitalet, Copenhagen Biocenter, Ole Maaloes Vej 5, DK-2200 Copenhagen N, Denmark, Department of Pathology, Henry Ford Health System, Detroit, Michigan 48202, and Department of Pharmacology, Wayne State University School of Medicine, Detroit, Michigan 48201.

In order to explore early events during the association of plasminogen activator inhibitor-1 (PAI-1) with its cofactor vitronectin, we have applied a robust strategy that combines protein engineering, fluorescence spectroscopy, and rapid reaction kinetics. Fluorescence stopped-flow experiments designed to monitor the rapid association of PAI-1 with vitronectin indicate a fast, concentration-dependent, biphasic binding of PAI-1 to native vitronectin but only a monophasic association with the somatomedin B (SMB) domain, suggesting that multiple phases of the binding interaction occur only when full-length vitronectin is present. Nonetheless, in all cases, the initial fast interaction is followed by slower fluorescence changes attributed to a conformational change in PAI-1. Complementary experiments using an engineered, fluorescently silent PAI-1 with non-natural amino acids showed that concomitant structural changes occur as well in native vitronectin. Furthermore, we have measured the effect of vitronectin on the rate of insertion of the reactive center loop into beta-sheet A of PAI-1 during reaction with target proteases. With a variety of PAI-1 variants, we observe that both full-length vitronectin and the SMB domain have protease-specific effects on the rate of loop insertion but that the two exhibit clearly different effects. These results support a model for PAI-1 binding to vitronectin in which the interaction surface extends beyond the region of PAI-1 occupied by the SMB domain. In support of this model are recent results that define a PAI-1-binding site on vitronectin that lies outside the somatomedin B domain (Schar, C. R., Blouse, G. E., Minor, K. H., and Peterson, C. B. (2008) *J. Biol. Chem.* 283, 10297-10309) and the complementary site on PAI-1 (Schar, C. R., Jensen, J. K., Christensen, A., Blouse, G. E., Andreasen, P. A., and Peterson, C. B. (2008) *J. Biol. Chem.* 283, 28487-28496).

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Pathology

Cankovic, M., J. Reher, J. Whiteley, R. J. Zarbo and D. Chitule (2009). "Rapid automated DNA-RNA extraction: Validation of quick gene 820 (QG) for blood and tissue specimen processing." *Mod Pathol* **22**(Suppl 1): 380A. [PDF Full-Text](#) - Scroll down to page 380A

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Pathology

Chitale, D., A. Botrell, K. M. Chen, L. Whiteley, L. Neimier, Z. G. Zhang, G. W. Divine, U. Raju and M. J. Worsham (2009). "Differential pattern of methylation within hormone receptor negative breast cancers." *Mod Pathol* **22**(Suppl 1): 33A. [PDF Full-Text](#) - Scroll down to page 33A

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Pathology

Jones, B. A., L. G. Bekeris, R. E. Nakhleh, M. K. Walsh, P. N. Valenstein and P. College of American (2009). "Physician satisfaction with clinical laboratory services: a College of American Pathologists Q-probes study of 138 institutions." *Arch Pathol Lab Med* **133**(1): 38-43. [PDF Full-Text](#)

Department of Pathology, Henry Ford Hospital, Detroit, MI 48202, USA. bjones2@hfhs.org

CONTEXT: Monitoring customer satisfaction is a valuable component of a laboratory quality improvement program. OBJECTIVE: To survey the level of physician satisfaction with hospital clinical laboratory services. DESIGN: Participating institutions provided demographic and practice information and survey results of physician satisfaction with defined aspects of clinical laboratory services, rated on a scale of 1 (poor) to 5 (excellent). RESULTS: One hundred thirty-eight institutions participated in this study and submitted a total of 4329 physician surveys. The overall satisfaction score for all institutions ranged from 2.9 to 5.0. The median overall score for all participants was 4.1 (10th percentile, 3.6; 90th percentile, 4.5). Physicians were most

satisfied with the quality/reliability of results and staff courtesy, with median values of excellent or good ratings of 89.9%. Of the 5 service categories that received the lowest percentage values of excellent/good ratings (combined scores of 4 and 5), 4 were related to turnaround time for inpatient stat, outpatient stat, routine, and esoteric tests. Surveys from half of the participating laboratories reported that 96% to 100% of physicians would recommend the laboratory to other physicians. The category most frequently selected as the most important category of laboratory services was quality/reliability of results (31.7%). CONCLUSIONS: There continues to be a high level of physician satisfaction and loyalty with clinical laboratory services. Test turnaround times are persistent categories of dissatisfaction and present opportunities for improvement.

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Pathology

Kartono, F., P. K. Shitabata, C. M. Magro and D. Rayhan (2009). "Discohesive malignant melanoma simulating a bullous dermatoses." J Cutan Pathol **36**(2): 274-9. [PDF Full-Text](#)

Henry Ford Macomb Hospital, Clinton Township, MI, USA.

A variety of clinical and histological presentations can accompany the evolution of malignant melanoma. Unusual cytological variants of malignant melanoma include balloon cell, signet ring cell, myxoid and other metaplastic changes. With the exception of a case of pemphigus-like changes associated with malignant melanoma in paraneoplastic pemphigus, acantholysis is not a common histopathological feature of malignant melanoma. We present two unique cases of malignant melanoma with varying degrees of extensive melanocytic discohesion in an acantholytic pattern mimicking pemphigus vulgaris, further referred to in this article as 'discohesive melanoma'. Routine direct immunofluorescence studies for pemphigus-related antibodies (IgG and C3) were negative. In one case, indirect immunofluorescence for desmoglein autoantibodies characteristic of pemphigus were negative, although positive antibodies to desmoglein 1 was detected using immunosorbent assay. The differential diagnoses and pitfalls in recognition of this unusual presentation of malignant melanoma along with possible pathogenetic mechanisms are discussed.

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Pathology

Lee, H., C. K. Ma, A. H. Ormsby and I. T. Shah (2009). "IgG and IgM immunostaining of inflammatory cells, histopathology and serology in 63 cases of overlap syndrome, autoimmune hepatitis and primary biliary cirrhosis, with special attention to overlap syndrome." Mod Pathol **22**(Suppl 1): 313A-314A. [PDF Full-Text](#) - Scroll down to page 313A

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Pathology

Lee, H. and K. Maeda (2009). "Hamartoma of the spleen." Arch Pathol Lab Med **133**(1): 147-51. [PDF Full-Text](#)

Department of Pathology and Laboratory Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA. hlee1@hfhs.org

Splenic hamartoma is a rare, benign vascular proliferation that is often found incidentally while working up other complaints or at autopsy. Women more commonly present with symptoms related to mass effect than men. Histologic findings consist of unorganized vascular channels of varying width, with intervening red pulp-like disorganized stroma with or without lymphoid follicles. The endothelial cells are similar to those of normal splenic sinuses. Although rendering a diagnosis can be difficult, endothelial cells that are positive for CD8 are a key feature that differentiate hamartoma from other vascular lesions of the spleen. Clinical, radiologic, and histologic correlation is essential to ensure this benign lesion is not mistaken for malignancy.

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Pathology

Linden, M. D. (2009). "Giant cell lesions of bone and soft tissues: Diagnostic value of immunohistochemistry." Mod Pathol **22**(Suppl 1): 18A. [PDF Full-Text](#) - Scroll down to page 18A

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Pathology

Meier, F. A., R. C. Varney, R. D'Angelo, A. Gandhi and R. J. Zarbo (2009). "A taxonomy of amended reports assesses impact of Henry Ford Production System [HFPS] a lean quality initiative in surgical pathology." Mod Pathol **22**(Suppl 1): 365A. [PDF Full-Text](#) - Scroll down to page 365A

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Pathology

Raghunathan, A., G. Sharma, L. Whiteley, J. A. Gutierrez and D. Chitale (2009). "Reverse transcriptase-polymerase chain reaction (RT-PCR) assay for detecting epidermal growth factor receptor variant-III (EGFRvIII) in glioblastomas." Mod Pathol **22**(Suppl 1): 334A. [PDF Full-Text](#) - Scroll down to page 334A

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Pathology

Raoufi, M., C. Ma, A. Ormsby, H. Vakil, K. Brown, M. A. Huang, D. Moonka and M. Abouljoud (2009). "The role of post-reperfusion biopsy (PRB) in the era of extended criteria donor (ECD): Clinicopathologic correlation and follow-up analysis of 50 liver transplant patients, a prospective study." Mod Pathol **22**(Suppl 1): 320A. [PDF Full-Text](#) - Scroll down to page 320A

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Pathology

Shamanna, R. K., L. J. Medeiros, L. Whiteley, D. S. Schultz, D. A. Chitale and K. V. Inamdar (2009). "Aurora-A kinase distinguishes ALK plus anaplastic large cell lymphoma from ALK negative and cutaneous ALCL among other T cell lymphomas: Analysis of 72 cases." Mod Pathol **22**(Suppl 1): 286A. [PDF Full-Text](#) - Scroll down to page 286A

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Pathology

Zhang, Z. S., R., U. Raju, A. Ormsby and D. Chitale (2009). "Does Nottingham Grade, MIB-1 labeling index (L1) predict recurrent score (RS) of oncotype DX (TM) assay?" Mod Pathol **22**(Suppl 1): 76A. [PDF Full-Text](#) - Scroll down to page 76A

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Pathology

Zuo, Y., S. A. Potthoff, T. J. Brolin, T. Myohanen, N. E. Rhaleb, O. A. Carretero, H. C. Yang, L. J. Ma and A. B. Fogo (2009). "Altered balance of thymosin beta 4 and Ac-SDKP exacerbates tubulointerstitial fibrosis." Mod Pathol **22**(Suppl 1): 306A. [PDF Full-Text](#) - Scroll down to page 306A

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Pharmacy

Jennings, D. L. and J. S. Kalus (2008). "Addition of cilostazol to aspirin and a thienopyridine for prevention of restenosis after coronary artery stenting: A meta-analysis." Circulation **118**(18 Suppl 2): S806.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Henry Ford Hospital, Detroit, MI

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Pulmonary

Jennings, J. H., B. Digiovine, D. Obeid and C. Frank (2009). "The Association Between Depressive Symptoms and Acute Exacerbations of COPD." Lung. EPub Ahead of Print. [PDF Full-Text](#)

Division of Pulmonary and Critical Care Medicine, Henry Ford Health System, K-17, 2799 W. Grand Blvd, Detroit, MI, 48202, USA, jjennin2@hfhs.org.

BACKGROUND: Depression is an important comorbidity for patients with chronic obstructive pulmonary disease (COPD). The association between depression and acute exacerbations of COPD is unknown. This study was designed to determine the frequency of COPD exacerbations in outpatients with and without depressive symptoms. METHODS: In this retrospective cohort study, patients with a primary diagnosis of COPD were followed for 1 year after discharge from a pulmonary rehabilitation program and the frequency of exacerbations was recorded. Upon completion of the program, all patients were administered the Short-Form 36 Health Survey (SF-36), which contains a mental health domain. Patients were classified as having depressive symptoms based on their domain score, which was separately validated in a second population of patients. RESULTS: Of the 194 patients with COPD who completed the pulmonary rehabilitation program, 32 (16.5%) had depressive symptoms. There were no differences in terms of age, race, pack-years, forced expiratory volume in 1 second (FEV(1)), 6-minute walk distance, body mass index, use of supplemental oxygen, use of inhaled steroids, or the Charlson Comorbidity Index between patients with and without depressive symptoms. Patients with depressive symptoms had more exacerbations in the following year (1.91 vs. 1.36; $p = 0.02$), were 2.8 times more likely to have ever had an exacerbation (95% confidence interval (CI), 1.1-7.3; $p = 0.03$), and suffered a first exacerbation earlier (148 days compared with 266 days; $p = 0.04$) than nondepressed patients. CONCLUSIONS: COPD patients with depressive symptoms have a significantly higher risk for exacerbations. Early screening for depression in patients with COPD may help identify those patients at higher risk for subsequent exacerbations.

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Sleep Center

Fava, M., K. Schaefer, C. B. Rockett, D. Amato and T. Roth (2008). "Differential sleep effects of eszopiclone treatment and discontinuation in patients with primary insomnia and insomnia co-existing with major depressive disorder (MDD) or generalized anxiety disorder (GAD)." J Sleep Res **17**(Suppl 1): 191. [PDF Full-Text](#) - Scroll down to page 191

Henry Ford Hospital, Detroit, MI

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Sleep Medicine

Kushida, C. A., A. S. Walters, P. Becker, S. G. Thein, T. Perkins, T. Roth, D. Canafax and R. W. Barrett (2009). "A randomized, double-blind, placebo-controlled, crossover study of XP13512/GSK1838262 in the treatment of patients iwth primary restless legs syndrome." Sleep **32**(2): 159-68. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, MI

Study Objective: To evaluate the efficacy and tolerability of XP13512/GSK1838262, an investigational nondopaminergic agent for the treatment of moderate-to-severe primary restless legs syndrome (RLS). Design: Randomized, double-blind, placebo-controlled, crossover trial.

Setting: Nine US clinical sites.

Patients: Thirty-eight treatment-naive subjects with RLS (mean +/- SD age 50.1 +/- 13.2 years).

Interventions: XP13512 1800 mg/day followed by placebo or placebo followed by XP13512 1800 mg/day for 14 days, with a 7-day washout between treatment periods.

Measurements and Results: The primary endpoint was mean change from baseline International RLS Study Group rating scale (IRLS) total score on Day 14, analyzed using analysis of variance with sequence, period, and treatment as fixed effects and subjects within sequence as a random effect. XP13512 significantly reduced IRLS total score on Day 14 compared with placebo (mean +/- SD: XP13512 - 12.1 +/- 6.5, placebo -1.9 +/- 6.3; $P < 0.0001$). Polysomnographic data showed that XP13512 significantly improved sleep architecture on Day 14 compared with placebo (mean +/- SD change from baseline sleep time [minutes]: stage 1: XP13512-9.8 +/- 23.9, placebo 0.4 +/- 23.2; adjusted $P < 0.0054$, nominal $P < 0.0001$; stage 3/4 (slow-wave sleep): XP13512 22.8 +/- 40.8, placebo 1.4 +/- 34.3; adjusted $P = 0.0092$, nominal $P = 0.0002$). The most frequently reported adverse events were somnolence (XP13512 30.6%, placebo 2.8%) and dizziness (XP13512 27.8%, placebo 5.6%).

Conclusions: XP13512 1800 mg/day significantly reduced RLS symptoms, improved sleep, and was generally well tolerated in subjects with moderate-to-severe primary RLS across 14 days of treatment.

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Sleep Medicine

Rajaratnam, S. M. W., M. H. Polymeropoulos, D. M. Fisher, T. Roth, C. Scott, G. Birznieks and E. B. Klerman (2009). "Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: Two randomised controlled multicentre trials." *Lancet* **373**(9662): 482-91. [PDF Full-Text](#)

Henry Ford Hospital, Detroit, MI

Background Circadian rhythm sleep disorders are common causes of insomnia for millions of individuals. We did a phase II study to establish efficacy and physiological mechanism, and a phase III study to confirm efficacy of the melatonin agonist tasimelteon (VEC-162) for treatment of transient insomnia associated with shifted sleep and wake time.

Methods We undertook phase II and phase III randomised, double-blind, placebo-controlled, parallel-group studies. In a phase II study, 39 healthy individuals from two US sites were randomly assigned to tasimelteon (10 [n=9], 20 [n=8], 50 [n=71], or 100 mg [n=71]) or placebo (n=8). We monitored individuals for 7 nights: 3 at baseline, 3 after a 5-h advance of sleep-wake schedule with treatment before sleep, and 1 after treatment; we measured plasma melatonin concentration for circadian phase assessment. In a phase III study, 411 healthy individuals from 19 US sites, who had transient insomnia induced in a sleep clinic by a 5-h advance of the sleep-wake schedule and a first-night effect in a sleep clinic, were given tasimelteon (20 [n=100], 50 [n=102], or 100 mg [n=106]) or placebo (n=103) 30 min before bedtime. Prespecified primary efficacy outcomes were polysomnographic sleep efficiency (phase II study), latency to persistent sleep (phase III study), and circadian phase shifting (phase II study). Analysis was by intention to treat. Safety was assessed in both studies. These trials are registered with ClinicalTrials.gov, numbers NCT00490945 and NCT00291187.

Findings In the phase II study, tasimelteon reduced sleep latency and increased sleep efficiency compared with placebo. The shift in plasma melatonin rhythm to an earlier hour was dose dependent. In the phase III study, tasimelteon improved sleep latency, sleep efficiency, and wake after sleep onset (ie, sleep maintenance). The frequency of adverse events was similar between tasimelteon and placebo.

Interpretation After an abrupt advance in sleep time, tasimelteon improved sleep initiation and maintenance concurrently with a shift in endogenous circadian rhythms. Tasimelteon may have therapeutic potential for transient insomnia in circadian rhythm sleep disorders.

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Sleep Medicine

Roehrs, T. and T. Roth (2008). "GABAA agents in insomnia pharmacotherapy: Novel therapeutic targets." *J Sleep Res* **17**(Suppl 1): 58-9. [PDF Full-Text](#) - Scroll down to page 58

Henry Ford Hospital, Detroit, MI

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Sleep Medicine

Roth, T., A. Lankford, V. Pitman, D. Clark, J. Werth, T. Stern and D. Maylebern (2008). "Non-restorative sleep: A distinct, stable component of insomnia associated with impaired daytime function." J Sleep Res **17**(Suppl 1): 14-5. [PDF Full-Text](#) - Scroll down to page 14

Henry Ford Hospital, Detroit, MI

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Sleep Medicine

Roth, T., W. Mccall, T. Wessel, D. Amato, W. Paska and M. Fava (2008). "Eszopiclone co-administered with fluoxetine for insomnia co-existing with major depressive disorder (MDD): A subgroup analysis." J Sleep Res **17**(Suppl 1): 191-2. [PDF Full-Text](#) - Scroll down to page 191

Henry Ford Hospital, Detroit, MI

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Surgery

Deeb, D., X. Gao, H. Jiang, S. A. Dulchavsky and S. C. Gautam (2009). "Oleanane Triterpenoid CDDO-Me inhibits growth and induces apoptosis in prostate cancer cells by independently targeting pro-survival Akt and mTOR." Prostate. Epub Ahead of Print. [PDF Full-Text](#)

Departments of Surgery, Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Synthetic triterpenoids are potent anticancer agents, but their therapeutic efficacy or mechanism of action for prostate cancer has not been investigated. The goal of this study was to determine the antitumor activity and the mechanism of action of methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate (CDDO-Me), a oleanane-derived synthetic triterpenoid for human prostate cancer cells. METHODS: The antitumor activity of CDDO-Me for hormone-refractory PC-3 (AR(-)) and C4-2 (AR(+)) prostate cancer cell lines was determined by effects on cell growth and induction of apoptosis, identification of molecular targets, and therapeutic efficacy in vivo in PC-3 xenograft model. RESULTS: CDDO-Me inhibited the growth and induced apoptosis in PC-3 and C4-2 cells at extremely low concentrations. The antitumor activity of CDDO-Me was associated with the inhibition of p-Akt, mammalian target of rapamycin (mTOR), and nuclear factor kappa B (NF-kappaB) signaling proteins and their downstream targets such as p-Bad and p-Foxo3a (Akt); p-S6K1, p-eIF-4E and p-4E-BP1 (mTOR); and COX-2, VEGF and cyclin D1(NF-kappaB). Silencing of Akt sensitized the PC-3 cells to CDDO-Me, whereas overexpression of Akt induced resistance to CDDO-Me. Targeted silencing of Akt showed that Akt does not regulate mTOR activation in PC-3 cells, but targeted silencing of mTOR sensitized PC-3 cells to CDDO-Me mediated growth inhibition. Further, treatment with CDDO-Me inhibited the growth of PC-3 xenografts in nude mice. CONCLUSIONS: This study demonstrated potent antitumor activity of CDDO-Me against prostate cancer cells both in vitro and in vivo. Data also identified Akt and mTOR as molecular targets of CDDO-Me in prostate cancer cells.

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Surgery

Paxton, J. H. and I. S. Rubinfeld (2009). "Medical errors education for students of surgery: a pilot study revealing the need for action." J Surg Educ **66**(1): 20-4. [Article Request Form](#)

Department of Surgery, Henry Ford Hospital, Detroit, Michigan.

BACKGROUND: Medical errors training is an important yet often overlooked aspect of surgical education. In response to a perceived deficiency in medical errors training at our institution, we implemented an educational session on medical errors concepts for the benefit of rotating medical students. MATERIALS AND METHODS:

Medical students completed the same 12-question test before and after the 90-minute educational session. Pretest and posttest scores were compared for evidence of enhanced understanding. No personal identifiers were used, and students were provided unlimited time to complete the tests. Six groups of medical students (who ranged from 5 to 8 students per session) completed the educational session. All sessions were moderated by the same surgical resident and attending surgeon, who used a standard slide presentation. Test scores were analyzed with SPSS statistical software (version 14.0; SPSS Inc., Cary, NC), which employed the paired samples t-test (alpha = 0.05). RESULTS: Test scores increased significantly from a pretest mean of 27.3% correct (3.28 of 12 possible, SD = 1.57) to a mean posttest score of 70.1% (8.41, SD = 1.52) ($p < 0.001$). CONCLUSIONS: This retrospective pilot study demonstrated that a brief educational intervention led to statistically significant improved performance on a general understanding of medical errors. The study also revealed the dearth of baseline knowledge in our participating medical students on the subject. We believe that these results underscore the need for action in providing improved and ongoing education in medical errors concepts to enhance medical student awareness and proactive handling of medical errors.

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Surgery

Rajda, C. and N. M. George (2009). "The effect of education and literacy levels on health outcomes of the elderly." *J Nurse Practitioners* 5(2): 115-9. [Article Request Form](#)

Carol Rajda is the trauma nurse coordinator for Henry Ford Hospital in Detroit, Michigan.

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Surgery

Vega, J., M. Vatca, N. Mikulandric, K. Neme, A. Hanbali and N. Janakiraman (2009). "The effect of donor cytomegalovirus (CMV) serologic status on CMV reactivation and survival in patients undergoing allogeneic stem cell transplantation." *Biol Blood Marrow Transplant* 15(Suppl 2): 109. [Article Request Form](#)

Henry Ford Hospital, Detroit, MI

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Urology

Elder, J. S. (2009). "Editorial Comment on: Nonoperative Management of Grade 5 Renal Injury in Children: Does It Have a Place?" *Eur Urol*. Epub Ahead of Print. [Article Request Form](#)

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, MI USA.

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Urology

Kiran, R. P., N. Pokala, M. Rottoli and V. W. Fazio (2009). "Is survival reduced for patients with anal cancer requiring surgery after failure of radiation? Analysis from a population study over two decades." *Am Surg* 75(2): 163-8. [PDF Full-Text](#)

Henry Ford Hospital, Department of Urology, Detroit, MI 48202

Chemoradiotherapy is the standard treatment for anal cancer. Surgery is reserved for failure of therapy, but there are limited data examining outcomes after surgery. From a prospective population-based database on radiation and surgical therapy, we compare outcomes for patients with anal cancer undergoing rectal resection after radiation with patients undergoing radiation alone. Patients undergoing surgical resection of the rectum after initial radiation (SRT) for squamous cell carcinoma of the anus, anal canal, cloacogenic zone, and overlapping lesions of the rectum and anal canal from 1983 to 2002 were identified from the Surveillance, Epidemiology and End Results database. Patient and tumor characteristics of SRT were compared with those of patients who underwent radiation alone (RT). Survival was calculated by the Kaplan-Meier test. There were 1202 patients undergoing RT and 48 patients undergoing SRT. RT and SRT had similar median age, gender, and grade of tumor. SRT had more patients with regional stage of disease (66.7 vs 42.4%, $P = 0.001$). Mean

survival for SRT was, however, similar to RT (103 vs 96 months, $P = 0.8$). For patients with localized stage, survival for SRT and RT was similar (105 vs 98 months, $P = 0.7$). For patients with regional stage, survival for SRT and RT was similar (95 vs 83 months, $P = 0.6$). The presence of regional disease appears to be associated with surgical resection after radiotherapy. Mean survival for such patients is comparable to that of patients undergoing radiation alone. Because radiation is combined with chemotherapy, this suggests that salvage surgery after failure of therapy results in outcomes comparable to combination therapy alone.

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Urology

Rogers, C. G., R. Laungani, A. Bhandari, L. S. Krane, D. Eun, M. N. Patel, R. Boris, A. Shrivastava and M. Menon (2009). "Maximizing Console Surgeon Independence during Robot-Assisted Renal Surgery by Using the Fourth Arm and TileProtrade mark." *J Endourol* **23**(1): 115-22.

Sladen Library has an electronic subscription, but the issue for this article is not available online at the time of this publication.

Vattikuti Urology Institute, Henry Ford Hospital, Detroit, Michigan.

Purpose: We describe multiple uses of the fourth robotic arm and TileProtrade mark on the da Vinci((R)) S surgical system to maximize console surgeon independence from the assistant during robot-assisted renal surgery. **Materials and Methods:** We prospectively evaluated the use of the fourth robotic arm and TilePro on the da Vinci S during robot-assisted radical nephrectomy (RRN) and robot-assisted partial nephrectomy (RPN). The fourth robotic arm was used to provide kidney retraction, place the renal hilum on stretch, control vascular structures, apply and remove bulldog clamps during partial nephrectomy, and secure renal capsular stitches. TilePro was used to project intraoperative ultrasonography and preoperative CT images onto the console screen. **Results:** From January 2006 to June 2008, 90 robot-assisted kidney procedures were performed, of which the fourth robotic arm was used in 46 cases (RRN, 18; RPN, 24; nephroureterectomy, 4). The fourth robotic arm facilitated consistent kidney retraction for dissection of the renal hilum and mobilization of the kidney. The robotic Hem-o-Lok clip applier effectively controlled renal hilar vessels during eight RPN cases and secured renal capsular stitches during two RPN cases. Bulldog clamps were successfully applied to the renal artery during RPN using the fourth arm in two cases. TilePro was used during 22 RPN cases to project intraoperative ultrasonographic images and preoperative CT images onto the console screen as a picture-on-picture image to guide tumor resection. **Conclusions:** Robotic instruments used with the fourth robotic arm may give the console surgeon greater independence from the assistant during robot-assisted kidney surgery by facilitating steps such as kidney retraction, hilar dissection, and vascular control. The TilePro feature of the da Vinci S can be used to project intraoperative ultrasonography and preoperative imaging onto the console screen, potentially guiding tumor localization and resection during RPN without the need to leave the console to view external images.

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