

Henry Ford Health System Publication List December 2008

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

Anesthesiology

Frogel, J., S. Vodur, D. Applefield, R. Kruba, J. Raman and N. Mitter (2008). "Case 6--2008. An unusual case of right ventricular failure after orthotopic heart transplantation." J Cardiothorac Vasc Anesth **22**(6): 913-9.

[PDF Full-Text](#)

Department of Anesthesiology, Henry Ford Hospital, Detroit, MI 48202, USA. jfrogel1@hfhs.org

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Anesthesiology

Kroll, H. R., D. Kim, M. J. Danic, S. S. Sankey, M. Gariwala and M. Brown (2008). "A randomized, double-blind, prospective study comparing the efficacy of continuous versus pulsed radiofrequency in the treatment of lumbar facet syndrome." J Clin Anesth **20**(7): 534-7.

[PDF Full-Text](#)

Department of Anesthesia K-4, Henry Ford Hospital, Detroit, MI 48202, USA.

STUDY OBJECTIVES: To compare the efficacy of continuous radiofrequency (CRF) thermocoagulation with pulsed radiofrequency (PRF) in the treatment of lumbar facet syndrome. **DESIGN:** Prospective, randomized, double-blinded study. **SETTING:** Ambulatory pain clinic at a level-I trauma center and teaching institution. **PATIENTS:** 50 ASA physical status I, II, and III patients, at least 18 years of age, scheduled to undergo CRF or PRF for lumbar back pain. **INTERVENTIONS:** Target facet joints were identified with oblique radiographic views. Continuous radiofrequency thermocoagulation was delivered at 80 degrees C for 75 seconds, while PRF was delivered at 42 degrees C with a pulse duration of 20 ms and pulse rate of two Hz for 120 seconds. **MEASUREMENTS:** Visual analog scale (VAS) pain assessment and Oswestry Low Back Pain and Disability Questionnaire (OSW) were administered at baseline and then at three months. Comparisons between groups and within groups were made of the relative percentage improvement in VAS and OSW scores. **MAIN RESULTS:** No significant differences in the relative percentage improvement were noted between groups in either VAS (P = 0.46) or OSW scores (P = 0.35). Within the PRF group, comparisons of the relative change over time for both VAS (P = 0.21) and OSW scores (P = 0.61) were not significant. However,

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within the CRF group, VAS ($P = 0.02$) and OSW scores ($P = 0.03$) showed significant improvement. CONCLUSIONS: Although there was no significant difference between CRF and PRF therapy in long-term outcome in the treatment of lumbar facet syndrome, there was a greater improvement over time noted within the CRF group.

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Biostatistics & Research Epidemiology

Wells, K., M. Pladevall, E. L. Peterson, J. Campbell, M. Wang, D. E. Lanfear and L. K. Williams (2008). "Race-ethnic differences in factors associated with inhaled steroid adherence among adults with asthma." Am J Respir Crit Care Med **178**(12): 1194-201.

[PDF Full-Text](#)

Department of Biostatistics and Research Epidemiology, Henry Ford Hospital, Detroit, MI 48202, USA.

RATIONALE: Adherence to inhaled corticosteroid (ICS) medication is known to be low overall, but tends to be lower among African-American patients when compared with white patients. OBJECTIVES: To understand the factors that contribute to ICS adherence among African-American and white adults with asthma. METHODS: Eligible individuals had a prior diagnosis of asthma, one or more ICS prescriptions, and were members of a large health maintenance organization in southeast Michigan. Individuals were sent a survey that included questions about internal factors (e.g., patient beliefs, knowledge, and motivation) and external factors (e.g., socioeconomic status, barriers to care, social support, and stressors) potentially related to ICS adherence. Adherence was calculated using electronic prescription and fill data. Stepwise regression was used to identify factors associated with adherence before and after stratifying by race-ethnicity. MEASUREMENTS AND MAIN RESULTS: Surveys were returned by 1,006 (56.3%) of 1,787 eligible patients. Adjusting for internal factors, but not external factors, diminished the relationship between race-ethnicity and ICS adherence. Among African-American patients, readiness to take ICS medication was the only internal or external factor significantly associated with ICS adherence; it explained 5.6% of the variance in adherence. Among white patients, perceived ICS necessity, ICS knowledge, doctors being perceived as the source of asthma control, and readiness to take medication were the internal factors associated with ICS adherence; these accounted for 19.8% of the variance in adherence. CONCLUSIONS: Factors associated with ICS adherence appear to differ between African-American and white patients, suggesting that group-specific approaches are needed to improve adherence.

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Bone & Joint Center

Bishop, J. L., S. K. Kline, K. J. Aalderink, R. Zauel and M. J. Bey (2008). "Glenoid inclination: In vivo measures in rotator cuff tear patients and associations with superior glenohumeral joint translation." J Shoulder Elbow Surg **Epub Ahead of Print**.

[PDF Full-Text](#)

Department of Orthopaedic Surgery, Bone and Joint Center, Henry Ford Hospital, Detroit, MI.

Glenoid inclination has been associated with rotator cuff tears and superior humeral translation, but the relationship between glenoid inclination and superior humeral translation has not been assessed in vivo. This study compared glenoid inclination between repaired and contralateral shoulders in 21 unilateral rotator cuff repair patients. As a secondary analysis, we assessed the relationship between glenoid inclination and in vivo superior humeral translation. Glenoid inclination was measured from patient-specific, computed tomography-based bone models. Glenohumeral joint motion was measured from biplane radiographs collected during coronal-plane abductions. Glenoid inclination was significantly lower for the rotator cuff tear shoulders (90.7 degrees) than the asymptomatic, contralateral shoulders (92.3 degrees , $P = .04$). No significant correlation existed between increased glenoid inclination and superior-inferior translation of the uninjured shoulder ($P > .30$). This study failed to support the theory that glenoid inclination is responsible for superior humeral translation and the development of subacromial impingement.

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Bone & Joint Center

Vaidya, R., A. Sethi, S. Bartol, M. Jacobson, C. Coe and J. G. Craig (2008). "Complications in the use of rhBMP-2 in PEEK cages for interbody spinal fusions." J Spinal Disord Tech **21**(8): 557-62.

[PDF Full-Text](#)

Department of Orthopedic Surgery, Henry Ford Hospital, Detroit, MI 48201, USA.

STUDY DESIGN: All patients of spinal interbody fusion using polyetheretherketone (PEEK) cages and recombinant human bone morphogenetic protein (rhBMP)-2 performed over a 16-month period were reviewed. **OBJECTIVE:** To determine the suitability of PEEK cages when used in conjunction with rhBMP-2 in interbody spinal fusion. **SUMMARY OF BACKGROUND DATA:** Bone morphogenetic proteins are increasingly being used in spinal fusion to promote osteogenesis. PEEK is a semicrystalline aromatic polymer that is used as a structural spacer to maintain the disc and foraminal height. Their use has led to increased and predictable rates of fusion. However, not many reports of the adverse effects of their use are available. **METHODS:** Fifty-nine consecutive patients of interbody spinal fusion in the cervical or lumbar spine using a PEEK cage and rhBMP-2 were followed for an average of 26 months after surgery. A clinical examination and a record of Oswestry Disability Index, Visual Analog Scale for pain, and a pain diagram were performed preoperatively and at every follow-up visit. All patients had plain radiographs carried out to assess fusion. Ten patients of lumbar spine fusion were additionally evaluated with a computed tomography scan. **RESULTS:** All cases demonstrated an appreciable amount of new bone formation by 6 to 9 months in the cervical spine and by 9 to 12 months in the lumbar spine. End plate resorption was visible radiologically in all cervical spine fusions and majority of lumbar fusions. Cage migration was observed to occur maximally in patients with transforaminal lumbar interbody fusion and posterior lumbar interbody fusion. Disc space subsidence was seen in both cervical and lumbar arthrodesis with the latter showing a lesser incidence, but with a greater degree of collapse. **CONCLUSIONS:** PEEK cages and rhBMP-2 when used in spinal fusion give consistently good fusion rates. However, the early role of BMP in the resorptive phase may cause loosening, cage migration, and subsidence.

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Bone & Joint Center

Yang, M., B. Zhang, L. Zhang and G. Gibson (2008). "Contrasting expression of membrane metalloproteinases, MT1-MMP and MT3-MMP, suggests distinct functions in skeletal development." Cell Tissue Res **333**(1): 81-90.

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Bone and Joint Center, Henry Ford Hospital, Detroit, MI 48202, USA.

Membrane-type 1 matrix metalloproteinase (MT1-MMP) is the most ubiquitous and widely studied of the membrane-type metalloproteinases (MT-MMPs). It was thus surprising to find no published data on chicken MT1-MMP. We report here the characterization of the chicken gene. Its low sequence identity with the MT1-MMP genes of other species, high GC content, and divergent catalytic domain explains the absence of data and our difficulties in characterizing the gene. The absence of structural features in the chicken gene that have been suggested to be critical for the activation of MMP-2 by MT1-MMP; for the effect of MT1-MMP on cell migration and for the recycling of MT1-MMP suggest these features are either not essential or that MT1-MMP does not perform these functions in chickens. Comparison of the expression of chicken MT1-MMP with MT3-MMP and with MMP-2 and MMP-13 has confirmed the previously recognized co-expression of MT1-MMP with MMP-2 and MMP-13 in fibrous and vascular tissues, particularly those surrounding the developing long bones in other species. By contrast, MT3-MMP expression differs markedly from that of MT1-MMP and of both MMP-2 and MMP-13. MT3-MMP is expressed by chondrocytes of the developing articular surface. Similar expression patterns of this group of MT-MMPs and MMPs have been observed in mouse embryos and suggest distinct and specific functions for MT1-MMP and MT3-MMP in skeletal development.

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Cardiology

Al-Mallah, M., J. Mohyi and K. Ananthasubramaniam (2008). "Inadvertent anastomosis of saphenous vein graft to a cardiac vein detected with coronary computed tomographic angiography." J Cardiovasc Comput Tomogr **2**(1): 61-3.

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Heart and Vascular Institute, Henry Ford Hospital, Detroit MI 48202, USA.

A 34-year-old man with a prior history of Hodgkin's disease and coronary artery bypass surgery for radiation-induced left main disease presented with persistent chest pain. Cardiac catheterization showed near simultaneous filling of the venous system during arterial injection and could not precisely delineate the insertion point of the vein graft anastomosis to the diagonal branch, and the patient was referred for coronary computed tomography angiography (CTA). CTA demonstrated that the anastomosis of the graft was with a cardiac vein. This case illustrates the valuable complementary role of both angiographic methodologies in confirming a complex anatomic diagnosis.

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Cardiology

Alqaisi, F., F. Al-Badarin, Z. Jaffery, L. Tzogias, M. Dawod, G. Jacobsen and K. Ananthasubramaniam (2008). "Prognostic predictors and outcomes in patients with abnormal myocardial perfusion imaging and angiographically insignificant coronary artery disease." J Nucl Cardiol **15**(6): 754-61.

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Henry Ford Hospital, Heart & Vascular Institute, 2799 W Grand Blvd, Detroit, MI 48202 USA

Background. Abnormal stress myocardial perfusion imaging studies (SMPI) with angiographically insignificant coronary artery disease (ICAD) have often been labeled "false positive" scans. We evaluated the prognostic predictors and outcomes in an unselected patient population having abnormal SMPI and ICAD (study group) over a 24 month period of follow-up.

Methods. Retrospective study of consecutive patients who had SMPI and subsequent coronary angiography showing ICAD within 6 months of index scan with matched control group with normal scans. Major Adverse Cardiac Events (MACE) were defined as the first occurrence of death or myocardial infarction (MI). Patients were followed up to 24 months from the time of their SMPI to identify the development of MACE.

Results. One hundred and twenty five patients formed the study group and one hundred and thirty six patients formed the control group. Over a two-year follow up, approximately 13% of the study group had MACE as compared to 4.2% in the control group ($P = .022$). Abnormal SMPI, EF < 40% and chronic kidney disease (GFR < 60 ml/min) were independent predictors of MACE in the study group. In multivariate analysis for MACE prediction, chronic kidney disease remained the sole independent predictor regardless of size or severity of perfusion abnormalities ($P = <.001$).

Conclusion. Patients with abnormal SMPI and ICAD have a 13% event rate of MACE over a two-year follow up. CKD seems a very important marker of a higher risk subgroup amongst such patients.

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Center for Health Promotion & Disease Prevention

Davis, R. M. (2008). "British American Tobacco ghost-wrote reports on tobacco advertising bans by the International Advertising Association and J J Boddewyn." Tob Control **17**(3): 211-4.

[PDF Full-Text](#)

Center for Health Promotion and Disease Prevention, Henry Ford Health System, One Ford Place, 5C, Detroit, MI 48823, USA. ron.davis@ama-assn.org

In 1983 and 1986, the International Advertising Association (IAA) published an original version and then a revision of a report entitled "Tobacco Advertising Bans and Consumption in 16 Countries," which were edited by J J Boddewyn, a marketing professor. The reports concluded that tobacco advertising bans have not been accompanied by any significant reduction in tobacco consumption. Opponents of tobacco advertising restrictions trumpeted the IAA reports in print materials, media communications and legislative hearings during the 1980s and beyond. A new analysis of tobacco industry documents and transcripts of tobacco litigation testimony reveals that British American Tobacco ghost-wrote the IAA reports and that the Tobacco Institute (the trade association then representing the major US cigarette manufacturers) helped to arrange for Boddewyn to present the findings to the US Congress and the media. Further research on tobacco industry documents and tobacco litigation transcripts should assess whether tobacco industry sources were responsible for ghost-writing other studies favourable to the industry.

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Center for Health Services Research

Tunceli, K., H. Zeng, Z. A. Habib and L. K. Williams (2009). "Long-term projections for diabetes-related work loss and limitations among U.S. adults." Diabetes Res Clin Pract **83**(1): e23-5.

[Article Request Form](#)

Center for Health Services Research, Henry Ford Hospital, Detroit, MI 48202, USA.

We used data from the U.S. National Health Interview Survey to estimate the effect of diabetes on labor market outcomes. In the year 2050 an estimated 1.46 million U.S. adults will not be working; 597,000 will be work disabled; and 780,000 will have work limitations as a result of diabetes.

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Dermatology

Chong, B. F. and H. K. Wong (2008). "Treatment of psoriasis with etanercept in a patient with a history of primary B-cell lymphoma." Clin Exp Dermatol **Epub Ahead of Print**.

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

Summary The use of immunobiologicals that suppress an overly active immune system in psoriasis carries with it the possibility of cancer development as a result of immunosuppression. Patients with a history of malignancy may be at risk for recurrence when treated with immunosuppressive agents. Moreover, autoimmune diseases, such as psoriasis, have been associated with an increased risk of lymphoma. Therefore, risk-benefit assessments must take into account the clinical severity and treatment of psoriasis. We describe a 59-year-old white man with a history of primary B-cell lymphoma, severe recalcitrant plaque-type psoriasis and psoriatic arthritis, who was started on etanercept for treatment of his psoriasis and psoriatic arthritis. The patient has a long history of remission of his lymphoma. After treatment, the patient experienced significant global improvement with essentially complete remission of the cutaneous lesions and arthritis, and had no recurrence of his lymphoma or other systemic complications while on etanercept after follow-up for > 3 years.

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Dermatology

Hexsel, C. L., B. H. Mahmoud, D. Mitchell, J. Rivard, M. Owen, F. M. Strickland, H. W. Lim and I. Hamzavi (2008). "A clinical trial and molecular study of photoadaptation in vitiligo." Br J Dermatol **Epub Ahead of Print**.

[PDF Full-Text](#)

Multicultural Dermatology Center, Department of Dermatology, Henry Ford Hospital, Detroit, MI 48202, U.S.A.

Background Photoadaptation to ultraviolet (UV) B phototherapy is due to both pigmentary and nonpigmentary influences. Objectives To measure photoadaptation in vitiliginous skin and to compare it with normal pigmented skin. Methods Seventeen patients with Fitzpatrick skin phototypes III-VI with vitiligo received six to nine UVB treatments, two to three times weekly. Minimal erythema dose (MED) testing was done at baseline and after all treatments; the percentage change in MED was analysed as a measure of photoadaptation. The percentage decrease in cyclobutane pyrimidine dimers (CPDs) over 24 h after a single exposure of 1 MED was analysed on vitiliginous and normal skin. Results The mean +/- SD percentage change in MED from before to after treatments was: treated vitiliginous skin 28.5 +/- 39.9% (P = 0.015), treated normal skin 35.9 +/- 49.9% (P = 0.015), untreated vitiliginous skin 11.9 +/- 22.6% (P = 0.070), untreated normal skin 25.1 +/- 41.3% (P = 0.041). Of these patients, two-thirds had a positive percentage change in MED (photoadaptation). The mean amount of CPDs induced per megabase of DNA immediately after exposure was significantly higher in vitiliginous skin. The mean +/- SD percentage decrease in CPDs (rate of repair) in 24 h was 35.7 +/- 26.8% in vitiliginous skin (P = 0.027) and 46.2 +/- 19.5% in normally pigmented skin (P = 0.001); no difference was noted in the repair in vitiliginous skin compared with normal skin (P = 0.4). Conclusions Photoadaptation in vitiliginous and normal skin was observed in two-thirds of patients. Vitiliginous skin had significantly more CPDs following UVB exposure; the rate of repair of UVB-induced DNA damage was equivalent to that in normal skin.

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Dermatology

Salama, H. and T. Shwayder (2008). "Eccrine nevus presenting as a hypopigmented patch." *Ped Dermat* **25**(6): 613-5.

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Henry Ford Hospital, Deptment of Dermatology, Detroit, MI 48202 USA

A 14-month-old Caucasian male presented with a hypopigmented patch associated with increased perspiration on the right side of his back, flank, and abdomen. Starch iodide test and biopsy revealed an eccrine nevus. The truncal presentation and light color both were unique presentations of this rare hamartoma.

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Diagnostic Radiology

Kamer, A. P., J. G. Craig, M. T. van Holsbeeck and M. Abdulhak (2008). "An Unusual Presentation of a Thoracic Vertebral Body Fracture in a Patient With Diffuse Idiopathic Skeletal Hyperostosis." *J Trauma* **Epub Ahead of Print**.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

From the Henry Ford Hospital, Detroit, Michigan.

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Diagnostic Radiology

Patel, M., F. Siddiqui, J. Y. Jin, T. Mikkelsen, M. Rosenblum, B. Movsas and S. Ryu (2008). "Salvage reirradiation for recurrent glioblastoma with radiosurgery: radiographic response and improved survival." *J Neurooncol* **Epub Ahead of Print**.

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Henry Ford Health System, Detroit, MI, USA, mpatel2@hfhs.org.

Purpose To determine the radiographic and clinical efficacy of stereotactic single dose radiosurgery (SRS) and fractionated stereotactic radiotherapy (FSRT) as salvage therapy for glioblastoma (GBM) at recurrence.

Methods Thirty-six patients with pathologically proven recurrent GBM were treated with salvage reirradiation by either SRS or FSRT between March of 2001 and August of 2006. Thirty-one patients had an initial diagnosis of GBM. Five patients had a malignant transformation. All patients had received radiotherapy with a dose of 50-60 Gy, a median 13.6 months prior to reirradiation (range: 0.8-119 months). At the time of recurrence, 26 patients were treated with SRS with a median dose of 18 Gy (range: 12-20 Gy). FSRT was performed in ten patients with a dose of 36 Gy in six fractions, twice weekly. Follow-up included MRI and clinical examination every 2 months. Results Median survival time after SRS was 8.5 months, compared to 7.4 months after FSRT ($P = 0.81$). Of 26 patients treated with SRS, radiographic tumor response or stable disease was observed in eight (35%) patients and tumor progression was seen in 18 (65%) patients. Of 10 patients treated by FSRT, radiographic tumor response or stable disease was observed in four (40%) patients and tumor progression was observed in four (40%) patients (two lost to follow-up). Patients who responded to treatment had statistically improved survival compared to non-responders, with median survival of 15.8 vs. 7.3 months ($P < 0.05$).

Conclusion Salvage reirradiation with SRS or FSRT for recurrent GBM results in radiographic response in a proportion of patients. Survival was significantly improved among patients who either responded or had stable disease after salvage reirradiation, compared to non-responders. Further study is warranted to investigate the method and time of reirradiation for recurrent GBM.

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Gastroenterology

Gordon, S. C. and K. E. Sherman (2008). "Treatment of HCV/HBV Coinfection: Releasing the Enemy Within." Gastroenterology **EPub Ahead of Print**.

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Henry Ford Health Systems, Detroit, Michigan.

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Gastroenterology

Moonka, D., K. A. Milkovich, B. Rodriguez, M. Abouljoud, M. M. Lederman and D. D. Anthony (2008). "Hepatitis C virus-specific T-cell gamma interferon and proliferative responses are more common in perihepatic lymph nodes than in peripheral blood or liver." J Virol **82**(23): 11742-8.

[PDF Full-Text](#)

Division of Gastroenterology, Transplant Surgery, Henry Ford Health System, Detroit, Michigan, USA.

The activation state, differentiation state, and functions of liver lymphocytes and perihepatic lymph nodes during chronic hepatitis C virus (HCV) infection are not well understood. Here, we performed phenotypic and functional analyses of freshly prepared lymphocytes isolated from the livers, perihepatic lymph nodes, and peripheral blood compartments of chronic HCV-infected and disease control subjects with end-stage liver disease undergoing liver transplantation. We measured lymphocyte subset frequency and memory T-cell gamma interferon (IFN-gamma) and proliferative responses to HCV peptide and control viral antigens in direct ex vivo assays. We found higher frequencies of CD4 cells in the lymph node compartment than in the other compartments for both HCV-infected and disease control subjects. Lymph node CD4 and CD8 cells less commonly expressed the terminal differentiation marker CD57, a finding consistent with an earlier differentiation state. In HCV-infected subjects, HCV-specific IFN-gamma-producing and proliferative responses were commonly observed in the lymph node fraction, while they were uncommonly observed in the peripheral blood or liver fractions. In contrast, control viral CD4 protein antigen and CD8 peptide antigen-specific IFN-gamma responses were commonly observed in the periphery and uncommonly observed in the lymph nodes of these same subjects. These findings are consistent with a selective defect in HCV-specific T-cell effector

function or distribution in patients with advanced chronic HCV infection. The high frequency of HCV-reactive T cells in perihepatic lymph nodes indicates that a failure to generate or sustain T-lymphocyte HCV reactivity is not responsible for the paucity of functional cells even in end-stage liver disease.

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Dabak, V. and P. Kuriakose (2008). "Thalidomide-induced severe hepatotoxicity." Cancer Chemother Pharmacol **EPub Ahead of Print**.

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Hypertension & Vascular Research

Ares, G. R., P. Caceres, F. J. Alvarez-Leefmans and P. A. Ortiz (2008). "cGMP decreases surface NKCC2 levels in the thick ascending limb: role of phosphodiesterase 2 (PDE2)." Am J Physiol Renal Physiol **295**(4): F877-87.

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Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, and Department of Physiology, Wayne State University, 2799 West Grand Blvd., Detroit, MI 48202, USA.

NaCl absorption in the medullary thick ascending limb of the loop of Henle (THAL) is mediated by the apical Na/K/2Cl cotransporter (NKCC2). Hormones that increase cGMP, such as nitric oxide (NO) and natriuretic peptides, decrease NaCl absorption by the THAL. However, the mechanism by which cGMP decreases NaCl absorption in THALs is not known. We hypothesized that cGMP decreases surface NKCC2 levels in the THAL. We used surface biotinylation to measure surface NKCC2 levels in rat THAL suspensions. We tested the effect of the membrane-permeant cGMP analog dibutyryl-cGMP (db-cGMP) on surface NKCC2 levels. Incubating THALs with db-cGMP for 20 min decreased surface NKCC2 levels in a concentration-dependent manner (basal=100%; db-cGMP 100 microM=77+/-7%; 500 microM=54+/-10% and 1,000 microM=61+/-8%). A different cGMP analog 8-bromo-cGMP (8-Br-cGMP) also decreased surface NKCC2 levels by 25%, (basal=100%; 8-Br-cGMP=75+/-5%). Incubation of isolated, perfused THALs with db-cGMP decreased apical surface NKCC2 labeling levels as measured by immunofluorescence and confocal microscopy. cGMP-stimulated phosphodiesterase 2 (PDE2) mediates the inhibitory effect of NO on NaCl absorption by THALs. Thus we examined the role of PDE2 and found that PDE2 inhibitors blocked the effect of db-cGMP on surface NKCC2. Also, a nonstimulatory concentration of db-cAMP blocked the cGMP-induced decrease in surface NKCC2. Finally, db-cGMP inhibited THAL net Cl absorption by 48+/-4%, and this effect was completely blocked by PDE2 inhibition. We conclude that cGMP decreases NKCC2 levels in the apical membrane of THALs and that this effect is mediated by PDE2. This is an important mechanism by which cGMP inhibits NaCl absorption by the THAL.

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Hypertension & Vascular Research

Herrera, M., N. J. Hong, P. A. Ortiz and J. L. Garvin (2009). "Endothelin-1 Inhibits Thick Ascending Limb Transport via Akt-stimulated Nitric Oxide Production." J Biol Chem **284**(3): 1454-60.

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Hypertension and Vascular Research Division, Henry Ford Hospital, Detroit, Michigan 48202.

Endothelin-1 inhibits sodium reabsorption in the thick ascending limb (THAL) via stimulation of nitric oxide (NO) production. The mechanism whereby endothelin-1 stimulates THAL NO is unknown. We hypothesized that endothelin-1 stimulates THAL NO production by activating phosphatidylinositol 3-kinase (PI3K), stimulating Akt activity, and phosphorylating NOS3 at Ser(1177). This enhances NO production and inhibits sodium transport. We measured 1) NO production by fluorescence microscopy using DAF2-DA, 2) Akt activity using a fluorescence resonance energy transfer-based Akt reporter, 3) phosphorylated NOS3 and Akt by Western blotting, and 4) NKCC2 activity by fluorescence microscopy. In isolated THAL, endothelin-1 (1 nmol/liter) increased NO production from 0.23 +/- 0.24 to 2.81 +/- 0.32 fluorescence units/min ($p < 0.001$; $n = 5$) but failed to stimulate NO production in THALs isolated from NOS3(-/-) mice. Wortmannin (150 nmol/liter), a PI3K inhibitor, reduced endothelin-1-stimulated NO by 83% (0.49 +/- 0.13 versus 3.31 +/- 0.49 fluorescence units/min for endothelin-1 alone; $p < 0.006$; $n = 5$). Endothelin-1 stimulated Akt activity by 0.16 +/- 0.02 arbitrary units as measured by fluorescence resonance energy transfer ($p < 0.001$; $n = 5$) and increased phosphorylation of Akt at Ser(473) by 56 +/- 11% ($p < 0.002$; $n = 7$). Dominant-negative Akt blocked endothelin-1-induced NO by 60 +/- 8% ($p < 0.001$ versus control; $n = 6$), and an Akt inhibitor had a similar effect. Endothelin-1 increased phosphorylation of NOS3 at Ser(1177) by 89 +/- 24% ($p < 0.01$; $n = 7$) but had no effect on Ser(633). Endothelin-1 inhibited NKCC2 activity, an effect that was blocked by dominant-negative Akt and NOS inhibition. We conclude that endothelin-1 stimulates THAL NO production by activating PI3K, stimulating Akt activity, and phosphorylating NOS3 at Ser(1177). This enhances NO production and inhibits sodium transport.

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Hypertension & Vascular Research

Liu, Y. H., M. A. D'Ambrosio, T. D. Liao, H. Peng, N. E. Rhaleb, U. Sharma, S. Andre, H. J. Gabius and O. A. Carretero (2008). "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 **Epub Ahead of Print**.

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Henry Ford Hospital.

Galectin-3 (Gal-3) is secreted by activated macrophages. In hypertension, Gal-3 is a marker for hypertrophic hearts prone to develop heart failure (HF). Gal-3 infused in pericardial sac leads to cardiac inflammation, remodeling and dysfunction. N-Acetyl-Seryl-Aspartyl-Lysyl-Proline (Ac-SDKP), a natural occurring tetrapeptide, prevents and reverses inflammation and collagen deposition in the heart in hypertension and HF post myocardial 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 TGFbeta/Smad3 signaling pathway. Adult male rats were divided into four groups and received the following intrapericardial infusion for 4 weeks: 1) vehicle (saline, $n = 8$), 2) Ac-SDKP (800 microg/kg/day, $n = 8$), 3) Gal-3 (12 microg/day, $n = 7$), and 4) Ac-SDKP + Gal-3 ($n = 7$). Left ventricular ejection fraction (LVEF), cardiac output (CO) 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 LV, 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 -dP/dt response to isoproterenol challenge, E/A ratio and LVEF. 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. Key words: Ac-SDKP, galectin-3, inflammation, cardiac dysfunction.

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Hypertension & Vascular Research

Ramseyer, V. D. and J. L. Garvin (2008). "Angiotensin II Decreases Nitric Oxide Synthase 3 Expression via Nitric Oxide and Superoxide in the Thick Ascending Limb." Hypertension **Epub Ahead of Print**.

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Hypertension and Vascular Research Division, Henry Ford Hospital, and the Department of Physiology, Wayne State University, Detroit, Mich.

NO produced by NO synthase type 3 (NOS3) in medullary thick ascending limbs (mTHALs) inhibits Cl(-) reabsorption. Acutely, angiotensin II stimulates thick ascending limb NO production. In endothelial cells, NO inhibits NOS3 expression. Therefore, we hypothesized that angiotensin II decreases NOS3 expression via NO in mTHALs. After 24 hours, 10 and 100 nmol/L of angiotensin II decreased NOS3 expression by 23±9% (n=6; P<0.05) and 50±5% (n=7; P<0.001), respectively, in primary cultures of rat mTHALs. NO synthase inhibition by 4 mmol/L of N(G)-nitro-L-arginine methyl ester hydrochloride prevented angiotensin II from decreasing NOS3 expression (Delta=-5±8%; n=5). In the presence of N(G)-nitro-L-arginine methyl ester hydrochloride, the addition of exogenous NO (1 micromol/L spermine NONOate) restored the angiotensin II-induced decreases in NOS3 expression (-22±6%; n=7; P<0.013). In addition, NO scavenging with 10 micromol/L of carboxy-PTIO abolished the effect of angiotensin II in NOS3 expression (Delta=-1±8% versus carboxy-PTIO alone; n=6). Angiotensin II increases superoxide, and superoxide scavenges NO. Thus, we tested whether scavenging superoxide enhances the angiotensin II-induced reduction in NOS3 expression. Surprisingly, treatment with 100 micromol/L of Tempol, a superoxide dismutase mimetic, blocked the angiotensin II-induced decrease in NOS3 expression (Delta=-3±7%; n=6). This effect was not because of increased hydrogen peroxide. We concluded that angiotensin II-induced decreases in NOS3 expression in mTHALs require both NO and superoxide. Decreased NOS3 expression by angiotensin II in mTHALs could contribute to increased salt retention observed in angiotensin II-induced hypertension.

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Hypertension & Vascular Research

Ren, Y., M. A. D'Ambrosio, J. L. Garvin, H. Wang and O. A. Carretero (2008). "Possible Mediators of Connecting Tubule Glomerular Feedback." [Hypertension](#) **EPub Ahead of Print**.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

Division of Hypertension and Vascular Research, Henry Ford Hospital, Detroit, Mich.

In the renal cortex, the connecting tubule (CNT) returns to the glomerular hilum and contacts the afferent arteriole (Af-Art). Increasing Na delivery to the CNT dilates the Af-Art by activating epithelial Na channels, a process that we call connecting tubule glomerular feedback (CTGF). However, the mediator(s) of CTGF are unknown. We tested the hypothesis that Na reabsorption by the CNT induces release of arachidonic acid metabolites that diffuse to and dilate the Af-Art. Microdissected rabbit Af-Arts and adherent CNTs were simultaneously microperfused. CTGF was measured as the increase in diameter of norepinephrine-precontracted Af-Arts in response to switching NaCl concentration in the lumen of the CNT from 10 to 80 mmol/L. Under control conditions, CTGF was repeatable and completely reversed norepinephrine-induced vasoconstriction. In the presence of 5,8,11,14-eicosatetraenoic acid, an inhibitor of arachidonic acid metabolism, CTGF was completely blocked (-0.7±0.3 versus 7.3±0.5 microm), suggesting that arachidonic acid metabolites mediate CTGF. Because both cyclooxygenase-derived prostaglandins and epoxygenase-derived epoxyeicosatrienoic acids are known vasodilatory arachidonic acid metabolites, we tested whether indomethacin or MS-PPOH (a cyclooxygenase and an epoxygenase inhibitor) could block CTGF. Both indomethacin and MS-PPOH partially blocked CTGF (2.3±0.8 versus 6.5±0.5 microm, and 2.9±0.8 versus 6.6±1.1 microm, respectively). When combined, they completely blocked CTGF (-0.4±0.3 versus 6.6±1.1 microm). We confirmed these findings by using the epoxyeicosatrienoic acid antagonist 14,15-EEZE. The combination of indomethacin plus 14,15-EEZE completely abolished CTGF (-0.3±0.2 versus 8.0±1.0 microm). We conclude that increasing Na concentrations in the CNT stimulate release of prostaglandins and epoxyeicosatrienoic acids, which mediate CTGF.

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Hypertension & Vascular Research

Ren, Y., M. A. D'Ambrosio, H. Wang, R. Liu, J. L. Garvin and O. A. Carretero (2008). "Heme oxygenase metabolites inhibit tubuloglomerular feedback (TGF)." [Am J Physiol Renal Physiol](#) **295**(4): F1207-12.

[PDF Full-Text](#)

Division of Hypertension and Vascular Research, Henry Ford Hospital, 2799 Grand Blvd., Detroit, MI 48202, USA.

Tubuloglomerular feedback (TGF) is the mechanism by which the macula densa (MD) senses increases in luminal NaCl concentration and sends a signal to constrict the afferent arteriole (Af-Art). The kidney expresses constitutively heme oxygenase-2 (HO-2) and low levels of HO-1. HOs release carbon monoxide (CO), biliverdin, and free iron. We hypothesized that renal HOs inhibit TGF via release of CO and biliverdin. Rabbit Af-Arts and attached MD were simultaneously microperfused in vitro. The TGF response was determined by measuring Af-Art diameter before and after increasing NaCl in the MD perfusate. When HO activity was inhibited by adding stannous mesoporphyrin (SnMP) to the MD perfusate, the TGF response increased from 2.1±0.2 to 4.1±0.4 microm (P=0.003, control vs. SnMP, n=7). When a CO-releasing molecule, (CORM-3; 50 microm), was added to the MD perfusate, the TGF response decreased by 41%, from 3.6±0.3 to 2.1±0.2 microm (P<0.001, control vs. CORM-3, n=12). When CORM-3 at 100 microm was added to the perfusate, it completely blocked the TGF response, from 4.2±0.4 to -0.2±0.3 microm (P<0.001, control vs. CORM-3, n=6). When biliverdin was added to the perfusate, the TGF response decreased by 79%, from 3.4±0.3 to 0.7±0.4 microm (P=0.001, control vs. biliverdin, n=6). The effects of SnMP and CORM-3 were not blocked by inhibition of nitric oxide synthase. We concluded that renal HO inhibits TGF probably via release of CO and biliverdin. HO regulation of TGF is a novel mechanism that could lead to a better understanding of the control of renal microcirculation and function.

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Hypertension & Vascular Research

Silva, G. B. and J. L. Garvin (2008). "TRPV4 mediates hypotonicity-induced ATP release by the thick ascending limb." Am J Physiol Renal Physiol **295**(4): F1090-5.

[PDF Full-Text](#)

Division of Hypertension and Vascular Research, Henry Ford Hospital, and Department of Physiology, School of Medicine, Wayne State University, 2799 W. Grand Blvd., Detroit, MI 48202, USA.

Extracellular ATP is an autocrine/paracrine factor that regulates renal function. Transient receptor potential vanilloid (TRPV) 4 is a cation channel that mediates release of autocrine/paracrine factors by acting as an osmosensor. The renal medulla, and therefore the thick ascending limb, is exposed to osmotic stress. We hypothesize that reduced osmolality stimulates ATP release from the thick ascending limb via transient receptor potential vanilloid (TRPV) 4 activation. We measured ATP release by medullary thick ascending limb suspensions after reducing bath osmolality from 350 to 323 mosmol/kgH₂O, using the luciferin-luciferase assay. Decreasing osmolality stimulated ATP release compared with control (38.9±7.2 vs. 2.4±1.0 pmol/mg protein; n=6, P<0.01). To examine the role of TRPV4, we used 1) Ca-free solutions, 2) a TRPV4 inhibitor, 3) small interfering (si) RNA against TRPV4, and 4) a TRPV4 activator. Removal of Ca completely blocked osmolality-induced ATP release (42.2±5.9 vs. 2.6±1.5 pmol/mg protein; n=6, P<0.01). In the presence of the TRPV4-selective inhibitor ruthenium red, osmolality-induced ATP release was blocked by 73% (56.4±19.9 vs. 8.8±2.3 pmol/mg protein; n=6; P<0.03). In vivo treatment of thick ascending limbs with siRNA against TRPV4 decreased osmolality-induced ATP release by 62% (31.5±3.4 vs. 12.4±1.1 pmol/mg protein; n=6; P<0.01), while reducing TRPV4 expression by 74% compared with the nontreated kidney. Treatment with scrambled siRNA did not affect TRPV4 expression and/or osmolality-induced ATP release. Finally, in the absence of changes in osmolality, the specific TRPV4 agonist 4alpha-PDD increased ATP release (3.6±0.9 vs. 25.4±7.4 pmol/mg protein; n=6; P<0.04). We concluded that decreases in osmolality stimulate ATP release by thick ascending limbs and this effect is mediated by TRPV4 activation.

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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 (2008). "The Kinin B1 Receptor Contributes to the Cardioprotective Effect of ACE Inhibitors and Angiotensin Receptor Blockers." Exp Physiol **Epub Ahead of Print**.

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Henry Ford Hospital.

Recent studies have shown that inhibition of angiotensin-converting enzyme (ACE) or angiotensin II receptor causes up-regulation of the B1 receptor (B1R). Here we tested the hypothesis that activation of B1R partially 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 controls, 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/day in drinking water) or ARB (valsartan, 40 mg/kg/day in drinking water) for 5 weeks. We found that 1) compared to WT mice, B1R^{-/-} that underwent sham surgery had slightly but significantly increased LV diastolic dimension, LV mass and myocyte size, whereas SBP, 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^{-/-}; and 3) ACEi and ARB improved cardiac function and remodeling 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

Jaffery, Z., R. Nowak, N. Khoury, G. Tokarski, D. E. Lanfear, G. Jacobsen and J. McCord (2008). "Myoglobin and troponin I elevation predict 5-year mortality in patients with undifferentiated chest pain in the emergency department." Am Heart J **156**(5): 939-45.

[PDF Full-Text](#)

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BACKGROUND: The long-term prognostic significance of elevated cardiac markers in an undifferentiated patient population with chest pain is unknown. **METHODS:** Serum troponin I (cTnI), creatine kinase-MB (CK-MB), and myoglobin were measured at presentation in 951 consecutive patients evaluated in the emergency department for possible acute coronary syndrome, and all-cause mortality was measured over 5 years. **RESULTS:** Final diagnoses included myocardial infarction in 70 (7.4%), unstable angina in 78 (8.2%), stable angina in 26 (2.7%), heart failure in 135 (14.2%), syncope in 61 (6.4%), arrhythmia in 62 (6.5%), and noncardiac diagnoses in 519 (54.6%). Our study population had a mean (+/-SD) age of 63 (+/-16), 434 (46%) were male, 774 (81%) were African American, 408 (43%) had known coronary artery disease, 647 (68%) had hypertension, 244 (26%) had diabetes mellitus, and 237 (25%) had a serum creatinine ≥ 1.5 mg/dL. At 5 years, there were 349 (36.7%) deaths. In a multivariate model with adjustment for baseline covariates, an elevated cTnI ≥ 1.0 ng/mL (hazard ratio [HR] 1.7, 95% CI 1.3-2.3) and myoglobin ≥ 200 ng/mL (HR 1.6, 95% CI 1.2-2.1), but not CK-MB ≥ 9.0 ng/mL (HR 0.9, 95% CI 0.6-1.3), remained independent predictors of all-cause mortality. Patients with both elevated cTnI and myoglobin had a particularly high mortality rate. **CONCLUSION:** Among patients evaluated in the emergency department for possible acute coronary syndromes, myoglobin and cTnI at presentation are powerful, independent predictors of long-term (5-year) prognosis.

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Internal Medicine

Kanjanauthai, S., T. Kanluen and P. Chareonthaitawee (2008). "Citalopram induced orsade de pointes, a rare life threatening side effect." Int J Cardiol **131**(1): E33-E34.

[PDF Full-Text](#)

Henry Ford Hospital, Department of Internal Medicine, Detroit, Michigan

Acquired Long QT syndrome is a disorder caused by medications, electrolyte imbalances, and drug interactions. This syndrome is associated with an increased risk of a characteristic life-threatening cardiac arrhythmia, known as torsade de pointes (TdP). In the setting of Long QT syndrome (LQTS), selective serotonin reuptake inhibitors (SSRIs) can precipitate TdP. We report the first case of LQTS and TdP induced by citalopram in the United States. After discontinuation of citalopram, the QT/QTc interval normalized after 3 days and resolved further episodes of TdP. Patients on citalopram should be monitored closely for QT/QTc interval to prevent torsade de pointes.

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Internal Medicine

Kanjanauthai, S., T. Kanluen and C. Ray (2008). "Pulmonary artery sarcoma masquerading as saddle pulmonary embolism." Heart Lung Circ **17**(5): 417-9.

[Article Request Form](#)

Department of Internal Medicine, Henry Ford Hospital, 2699 West Grand Boulevard, CFP-1, Detroit, MI 48202, USA. somsupha@hotmail.com

Pulmonary artery sarcoma is a highly malignant tumour. Therefore, making the diagnosis is very important. We describe a case which presented with dyspnea on exertion and was initially diagnosed as saddle pulmonary embolism per CT thorax with contrast. Despite adequate anticoagulation, symptoms still progressed. Follow-up CT thorax showed an extension of the presumed filling defect or clots into the left main pulmonary artery with new lung nodules. This prompted suspicion that this may not be a pulmonary embolism. Biopsy of the lung nodule revealed high grade soft tissue sarcoma with primary source from the pulmonary artery. Our case highlights that pulmonary artery sarcoma should always be included in the differential diagnosis of pulmonary embolism especially, if symptoms still progress while on adequate anticoagulation, or any pulmonary nodules develop on follow-up exam.

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Nephrology

Sidawy, A. N., L. M. Spergel, A. Besarab, M. Allon, W. C. Jennings, F. T. Padberg, M. H. Murad, V. M. Montori, A. M. O'Hare, K. D. Calligaro, R. A. Macsata, A. B. Lumsden and E. Ascher (2008). "The Society for Vascular Surgery: Clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access." J Vasc Surg **48**: S2-S25.

[PDF Full-Text](#)

Henry Ford Hosp, Division of Nephrology & Hypertension, Detroit, MI 48202 USA

Recognizing the impact of the decision making by the dialysis access surgeon on the successful placement of autogenous arteriovenous hemodialysis access, the Society for Vascular Surgery assembled a multispecialty panel to develop practice guidelines on arteriovenous access placement and maintenance with the aim of maximizing the percentage and functionality of autogenous arteriovenous accesses that are placed. The Society commissioned the Knowledge and Encounter Research Unit of the Mayo Clinic College of Medicine, Rochester, Minnesota, to systematically review the available evidence in three main areas provided by the panel: timing of referral to access surgeons, type of access placed, and effectiveness of surveillance. The panel then formulated practice guidelines in seven areas: timing of referral to the access surgeon, operative strategies to maximize the placement of autogenous arteriovenous accesses, first choice for the autogenous access, choice of arteriovenous access when a patient is not a suitable candidate for a forearm autogenous access, the role of monitoring and surveillance in arteriovenous access management, conversion of a prosthetic arteriovenous access to a secondary autogenous arteriovenous access, and management of the nonfunctional or failed arteriovenous access. For each of the guidelines, the panel stated the recommendation or suggestion, discussed the evidence or opinion upon which the recommendation or suggestion was made, detailed the values and preferences that influenced the group's decision in formulating the relevant guideline,

and discussed technical remarks related to the particular guideline. In addition, detailed information is provided on various configurations of autogenous and prosthetic accesses and technical tips related to their placement.

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Neurology

Athiraman, H., Q. Jiang, G. Liang Ding, L. Zhang, Z. Gang Zhang, L. Wang, A. S. Arbab, Q. Li, S. Panda, K. Ledbetter, A. M. Rad and M. Chopp (2008). "Investigation of relationships between transverse relaxation rate, diffusion coefficient, and labeled cell concentration in ischemic rat brain using MRI." Magn Reson Med **EPub Ahead of Print**.

[Article Request Form](#)

Department of Neurology, Henry Ford Health System, Detroit, Michigan, USA.

MRI has been used to evaluate labeled cell migration and distribution. However, quantitative determination of labeled cell concentration using MRI has not been systematically investigated. In the current study, we investigated the relationships between labeled cell concentration and MRI parameters of transverse relaxation rate, $R(2)$, and apparent diffusion coefficient (ADC), in vitro in phantoms and in vivo in rats after stroke. Significant correlations were detected between iron concentration or labeled cell concentration and MRI measurements of $R(2)$, ADC, and $ADC \times R(2)$ in vitro. In contrast, in vivo labeled cell concentration did not significantly correlate with $R(2)$, ADC, and $ADC \times R(2)$. A major factor for the absence of a significant correlation between labeled cell concentration and MRI measurements in vivo may be attributed to background effects of ischemic tissue. By correcting the background effects caused by ischemic damage, $\Delta R(2)$ (difference in $R(2)$ values in the ischemic tissue with and without labeled cells) exhibited a significant correlation to labeled cell concentration. Our study suggests that MRI parameters have the potential to quantitatively determine labeled cell concentration in vivo.

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Neurology

Bosomtvi, A., Q. Jiang, G. L. Ding, L. Zhang, Z. G. Zhang, M. Lu, J. R. Ewing and M. Chopp (2008). "Quantitative evaluation of microvascular density after stroke in rats using MRI." J Cereb Blood Flow Metab **28**(12): 1978-87.

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

We investigated vascular changes after stroke using magnetic resonance imaging (MRI) microvascular density (MVD) measurement. $T(2)$ and $T(2)^*$ were measured in eight rats before and after injecting an intravascular superparamagnetic iron oxide contrast agent to derive the corresponding transverse relaxation shift. Reliability of MRI for measurement of MVD was compared with corresponding sections immunostained with von Willebrand factor (vWF) 2 weeks after stroke. The intracorrelation coefficient (ICC) and its 95% lower bound (LB) was high in the ischemic recovery region (ICC=0.753), moderate in the contralateral area of normal brain tissue (ICC=0.70), and low in the ischemic core (ICC=0.24). A very good agreement (ICC=0.85) and correlation ($r=0.90$) were observed using only the recovery region and normal contralateral hemisphere (ICC=0.85; 95% LB=0.78; $P<0.05$). The mean MRI MVD in the center of the core lesion (26 ± 9 per mm^2) was lower than in the recovery region (209 ± 60 per mm^2) or contralateral normal hemisphere (313 ± 32 per mm^2). However, large errors in MRI MVD were encountered in the ischemic core. Our data demonstrate that MRI MVD measurements can quantitatively evaluate microvascular changes in the brain tissue after stroke, if the MVD is not extremely low as in the ischemic core.

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Neurology

Chopp, M. and Y. Li (2008). "Treatment of stroke and intracerebral hemorrhage with cellular and pharmacological restorative therapies." Acta Neurochir Suppl **105**: 79-83.

[Article Request Form](#)

Department of Neurology, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202, USA. chopp@neuro.hfh.edu

We describe some of our studies on use of neuro-restorative agents for treatment of neural injury. We focus on cell-based therapies and select from a variety of statins. In addition, we show that cell-based and pharmacological-based therapies enhance brain plasticity and promote recovery of function after stroke and intracerebral hemorrhage (ICH). Injured brain recapitulates ontogeny. Cerebral tissue around the infarction expresses developmental genes, many of which are present only during embryonic or neonatal stages of development. Brain response to injury undergoes remodeling with induction of angiogenesis, neurogenesis, and synaptogenesis. The attempt at remodeling, although expressed as a partial improvement in patients with stroke and ICH, is clearly insufficient to promote substantial recovery in many patients. The goal of restorative therapies should be to activate and amplify this endogenous restorative brain plasticity process to potentiate functional recovery. The logic of restorative therapy is to treat intact or marginally compromised tissue and not injured or dying tissue. Thus, these treatments can be made available for all neurological injury. Once demonstrated to be effective for treatment of a large middle cerebral artery occlusion (MCAo), these restorative treatments can be applied to many types of injury, including ICH, traumatic brain injury, and neurodegenerative disease such as experimental autoimmune encephalomyelitis and multiple sclerosis.

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Neurology

Chopp, M., Y. Li and Z. G. Zhang (2008). "Mechanisms Underlying Improved Recovery of Neurological Function After Stroke in the Rodent After Treatment With Neurorestorative Cell-Based Therapies." [Stroke](#) **EPub Ahead of Print**.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

From the Department of Neurology, Henry Ford Hospital, Detroit; and the Department of Physics, Oakland University, Rochester, Mich.

We discuss the mechanisms of action underlying the beneficial effects of treating ischemic stroke in the rodent with exogenously administered cells. The essential hypothesis proposed is that the administered cells enhance recovery of neurological function by stimulating the production of restorative factors by parenchymal cells. These activated endogenous brain cells evoke white matter remodeling in the brain and the spinal cord and generate microenvironments within the injured brain that amplify brain plasticity and lead to improvement in neurological function poststroke.

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Neurology

Lewitt, P. A. (2008). "Levodopa for the treatment of Parkinson's disease." [N Engl J Med](#) **359**(23): 2468-76.

[PDF Full-Text](#)

Department of Neurology, Henry Ford Hospital, and the Department of Neurology, Wayne State University School of Medicine, Detroit, USA. palewitt@ameritech.net

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Neurology

Mahmood, A., A. Goussev, D. Lu, C. Qu, Y. Xiong, H. Kazmi 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](#) **EPub Ahead of Print**.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

Department of Neurosurgery, Henry Ford Health System , Detroit, Michigan., Department of Psychiatry, State University of New York at Brooklyn , Brooklyn, New York., Department of Neurology, Henry Ford Health System , Detroit, Michigan ., Department of Physics, Oakland University , Rochester, Michigan .

Abstract 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 0.5 mg of simvastatin combined with 2 x 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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Neurology

Nuwer, M. R., G. L. Barkley, G. J. Esper, P. D. Donofrio, J. P. Szaflarski and T. R. Swift (2008). "The U.S. health care system, Part 2: Proposals for improvement and comparison to other systems." Neurology **71**(23): 1914-20.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

Henry Ford Hospital, Department of Neurology, Detroit, Michigan

In the search for a universal, high quality, affordable health care system, Americans seek to identify and correct a series of current problems. In part one of this two-part series, we presented problems along with some suggested actions. This second part presents other health care systems in Europe and Canada. These different systems provide universal care and at a lower cost than in the United States. Further domestic proposals are presented from the Massachusetts plan and positions from US presidential candidates. These systems and proposals raise ideas about possible changes in the US health care system. Knowledge of these issues and other health care systems will help foster a meaningful dialog about changes in the US health care system.

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Neurology

Nuwer, M. R., G. J. Esper, P. D. Donofrio, J. P. Szaflarski, G. L. Barkley and T. R. Swift (2008). "The U.S. health care system, Part 1: Our current system." Neurology **71**(23): 1907-13.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

Henry Ford Hospital, Department of Neurology, Detroit, Michigan

The US health care crisis is of great concern to American neurologists. The United States has the world's most expensive health care system yet one-sixth of Americans are uninsured. The cost and volume of procedures is expanding, while reimbursement for office visits is declining. Pharmaceutical costs, durable goods, and home health care are growing disproportionately to other services. Carriers spend more for their own administration and profit than on payments to physicians. This first article on the US health care system identifies problems and proposes solutions, many of which are championed by the American Academy of Neurology through its legislative and regulatory committees.

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Neurology

Santra, M., S. Santra, C. Roberts, R. L. Zhang and M. Chopp (2009). "Doublecortin induces mitotic microtubule catastrophe and inhibits glioma cell invasion." J Neurochem **108**(1): 231-45.

[PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Detroit, Michigan, USA.

Doublecortin (DCX) is a microtubule (MT) binding protein that induces growth arrest at the G2-M phase of cell cycle in glioma and suppresses tumor xenograft in immunocompromised hosts. DCX expression was found in neuronal cells, but lacking in glioma cells. We tested the hypothesis that DCX inhibits glioma U87 cell mitosis and invasion. Our data showed that DCX synthesizing U87 cells underwent mitotic MT spindle catastrophe in a neurabin II dependent pathway. Synthesis of both DCX and neurabin II were required to induce apoptosis in U87 and human embryonic kidney 293T cells. In DCX expressing U87 cells, association of phosphorylated DCX with protein phosphatase-1 (PP1) in the cytosol disrupted the interaction between kinesin-13 and PP1 in the nucleus and yielded spontaneously active kinesin-13. The activated kinesin-13 caused mitotic MT catastrophe in spindle checkpoint. Phosphorylated-DCX induced depolymerization of actin filaments in U87 cells, down-regulated matrix metalloproteinases-2 and -9, and inhibited glioma U87 cell invasion in a neurabin II dependent pathway. Thus, localization of the DCX-neurabin II-PP1 complex in the cytosol of U87 tumor cells inhibited PP1 phosphatase activities leading to anti-glioma effects via (1) mitotic MT spindle catastrophe that blocks mitosis and (2) depolymerization of actin that inhibits glioma cell invasion.

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Neurology

Sorenson, E. J., A. J. Windbank, J. N. Mandrekar, W. R. Bamlet, S. H. Appel, C. Armon, P. E. Barkhaus, P. Bosch, K. Boylan, W. S. David, E. Feldman, J. Glass, L. Gutmann, J. Katz, W. King, C. A. Luciano, L. F. McCluskey, S. Nash, D. S. Newman, R. M. Pascuzzi, E. Pioro, L. J. Sams, S. Scelsa, E. P. Simpson, S. H. Subramony, E. Tiryaki and C. A. Thornton (2008). "Subcutaneous IGF-1 is not beneficial in 2-year ALS trial." Neurology **71**(22): 1770-5.

Sladen has electronic subscription. Issue for this article not available online at the time of this publication.

Henry Ford Medical Center, Detroit, MI USA

Background: Previous human clinical trials of insulin-like growth factor type I (IGF-1) in amyotrophic lateral sclerosis (ALS) have been inconsistent. This phase III, randomized, double-blind, placebo-controlled study was undertaken to address whether IGF-1 benefited patients with ALS.

Methods: A total of 330 patients from 20 medical centers were randomized to receive 0.05 mg/kg body weight of human recombinant IGF-1 given subcutaneously twice daily or placebo for 2 years. The primary outcome measure was change in their manual muscle testing score. Secondary outcome measures included tracheostomy-free survival and rate of change in the revised ALS functional rating scale. Intention to treat analysis was used.

Results: There was no difference between treatment groups in the primary or secondary outcome measures after the 2-year treatment period.

Conclusions: Insulin-like growth factor type I does not provide benefit for patients with amyotrophic lateral sclerosis.

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Neurology

Wang, L., M. Chopp, R. L. Zhang, L. Zhang, Y. Letourneau, Y. F. Feng, A. Jiang, D. C. Morris and Z. G. Zhang (2008). "The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke." Neuroscience **Epub Ahead of Print**.

[PDF Full-Text](#)

Department of Neurology, Henry Ford Health Sciences Center, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

Molecular mechanisms by which stroke increases neurogenesis have not been fully investigated. Using neural progenitor cells isolated from the subventricular zone (SVZ) of the adult rat subjected to focal cerebral ischemia, we investigated the Notch pathway in regulating proliferation and differentiation of adult neural progenitor cells after stroke. During proliferation of neural progenitor cells, ischemic neural progenitor cells exhibited substantially increased levels of Notch, Notch intracellular domain (NICD), and hairy enhancer of split (Hes) 1, which was associated with a significant increase of proliferating cells. Blockage of the Notch pathway by short interfering ribonucleic acid (siRNA) against Notch or a gamma secretase inhibitor significantly reduced Notch, NICD and Hes1 expression and cell proliferation induced by stroke. During differentiation of neural progenitor cells, Notch and Hes1 expression was downregulated in ischemic neural progenitor cells, which was coincident with a significant increase of neuronal population. Inhibition of the Notch pathway with a gamma secretase inhibitor further substantially increased neurons, but did not alter astrocyte population in ischemic neural progenitor cells. These data suggest that the Notch signaling pathway mediates adult SVZ neural progenitor cell proliferation and differentiation after stroke.

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Neurosurgery

Jiang, W., C. Xiang, S. Cazacu, C. Brodie and T. Mikkelsen (2008). "Insulin-like growth factor binding protein 7 mediates glioma cell growth and migration." Neoplasia **10**(12): 1335-42.

[PDF Full-Text](#)

Hermelin Brain Tumor Center, Department of Neurosurgery, Henry Ford Hospital, Detroit, MI 48202, USA.

Insulin-like growth factor binding protein 7 (IGFBP-7) is the only member of the IGFBP superfamily that binds strongly to insulin, suggesting that IGFBP-7 may have different functions from other IGFBPs. Unlike other IGFBPs, the expression and functions of IGFBP-7 in glioma tumors have not been reported. Using cDNA microarray analysis, we found that expression of IGFBP-7 correlated with the grade of glioma tumors and the overall patient survival. This finding was further validated by real-time reverse transcription-polymerase chain reaction and Western blot analysis. We used RNAi to examine the role of IGFBP-7 in glioma cells, inhibiting IGFBP-7 expression by short interfering RNA transfection. Cell proliferation was suppressed after IGFBP-7 expression was inhibited for 5 days, and glioma cell growth was stimulated consistently by the addition of recombinant IGFBP-7 protein. Moreover, glioma cell migration was attenuated by IGFBP-7 depletion but enhanced by IGFBP-7 overexpression and addition. Overexpression of AKT1 in IGFBP-7-overexpressed cells attenuated the IGFBP-7-promoted migration and further enhanced inhibition of IGFBP-7 depletion on the migration. Phosphorylation of AKT and Erk1/2 was also inversely regulated by IGFBP-7 expression. These two factors together suggest that IGFBP-7 can regulate glioma cell migration through the AKT-ERK pathway, thereby playing an important role in glioma growth and migration.

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Neurosurgery

Reardon, D. A., K. L. Fink, T. Mikkelsen, T. F. Cloughesy, A. O'Neill, S. Plotkin, M. Glantz, P. Ravin, J. J. Raizer, K. M. Rich, D. Schiff, W. R. Shapiro, S. Burdette-Radoux, E. J. Dropcho, S. M. Wittemer, J. Nippgen, M. Picard and L. B. Nabors (2008). "Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme." J Clin Oncol **26**(34): 5610-7.

[PDF Full-Text](#)

Henry Ford Hospital, Detroit, Michigan

Purpose

Cilengitide, an inhibitor of alpha v beta 3 and alpha v beta 5 integrin receptors, demonstrated minimal toxicity and durable activity across a wide range of doses administered to adults with recurrent glioblastoma multiforme (GBM) in a prior phase I study. The current multicenter phase II study was conducted to evaluate the activity and safety of cilengitide in GBM patients at first recurrence.

Patients and Methods

Eligible patients were randomly assigned to receive either 500 or 2,000 mg of cilengitide twice weekly on a continuous basis. Patients were assessed every 4 weeks. The primary end point was 6-month progression-free survival (PFS) rate. Secondary end points included PFS, overall survival (OS), and radiographic response, as well as quality-of-life and pharmacokinetic assessments.

Results

Eighty-one patients were enrolled, including 41 on the 500-mg arm and 40 on the 2,000-mg arm. The safety profile of cilengitide was excellent, with no significant reproducible toxicities observed on either arm. Antitumor activity was observed in both treatment cohorts but trended more favorably among patients treated with 2,000 mg, including a 6-month PFS of 15% and a median OS of 9.9 months.

Conclusion

Cilengitide monotherapy is well tolerated and exhibits modest antitumor activity among recurrent GBM patients. Additional studies integrating cilengitide into combinatorial regimens for GBM are warranted.

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Otolaryngology

Sethi, S., M. Lu, A. Kapke, M. S. Benninger and M. J. Worsham (2008). "Patient and tumor factors at diagnosis in a multi-ethnic primary head and neck squamous cell carcinoma cohort." J Surg Oncol **EPub Ahead of Print**.

[PDF Full-Text](#)

Department of Otolaryngology/Head and Neck Surgery, Henry Ford Health Systems, Detroit, Michigan.

BACKGROUND: A long-term objective is to refine patient diagnosis and prognosis to address heterogeneity in head and neck squamous cell carcinoma (HNSCC) through incorporation of patient and tumor factors. This study examined histopathology and demographic variables at primary diagnosis (early vs. late stage) in a HNSCC patient population with a higher than usual percentage of African American (AA) subjects. **METHODS:** The primary HNSCC cohort was drawn from a diverse patient population and constructed through re-review of the primary biopsy. Nine specific histopathology and patient factors (race, gender, age) at primary HNSCC diagnosis were evaluated. Logistic regression analyses incorporated univariate and multivariable modeling. **RESULTS:** Race, gender, pattern of invasion, tumor necrosis, perineural invasion, site, and tumor grade were included in the first multivariable model. The final multivariable model retained gender, race, grade, site, and perineural invasion as independent risk factors for late stage with goodness-of-fit, the area under the curve (AUC), as 0.691. **CONCLUSIONS:** This report emphasizes patient and tumor characteristics of race, gender,

site, perineural invasion, grade, and pattern of invasion as independent factors of advanced stage HNSCC. Pattern of invasion and necrosis are also important tumor characteristics of late stage disease. These factors may offer clinical perspectives when evaluating patients with indeterminate stage.

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Otolaryngology

Stephen, J. K., K. M. Chen, M. Raitanen, S. Grenman and M. J. Worsham (2009). "DNA hypermethylation profiles in squamous cell carcinoma of the vulva." Int J Gynecol Pathol **28**(1): 63-75.

[PDF Full-Text](#)

Department of Otolaryngology/Head and Neck Research, Henry Ford Hospital, Detroit, Michigan 48202, USA.

Gene silencing through promoter hypermethylation is a growing concept in the development of human cancers. In this study, we examined the contribution of aberrant methylation of promoter regions in methylation-prone tumor suppressors to the pathogenesis of vulvar cancer. Thirteen cell lines from 12 patients with squamous cell carcinoma of the vulva were evaluated for aberrant methylation status and gene copy number alterations, concomitantly, using the methylation-specific multiplex ligation-dependent probe amplification assay. Of the 22 tumor suppressor genes examined, aberrant methylation was observed for 9 genes: tumor protein p73 (TP73), fragile histidine triad (FHIT), von Hippel-Lindau (VHL), adenomatous polyposis coli (APC), estrogen receptor 1 (ESR1), cyclin-dependent kinase inhibitor 2B (CDKN2B), death-associated protein kinase 1 (DAPK1), glutathione S-transferase pi (GSTP1), and immunoglobulin superfamily, member 4 (IGSF4). The most frequently methylated genes included TP73 in 9 of 13 cell lines, and IGSF4, DAPK1, and FHIT in 3 of 13 cell lines. Methylation-specific polymerase chain reaction was performed for TP73 and FHIT to confirm aberrant methylation by methylation-specific multiplex ligation-dependent probe amplification. In the context of gene copy number and methylation status, both copies of the TP73 gene were hypermethylated. Loss or decreased mRNA expression of TP73 and IGSF4 by reverse transcription polymerase chain reaction confirmed aberrant methylation. Frequent genetic alterations of loss and gain of gene copy number included gain of GSTP1 and multiple endocrine neoplasia type 1 (MEN1), and loss of malignant fibrous histiocytoma amplified sequence 1 (MFHAS1) and IGSF4 in over 50% of the squamous cell carcinoma of the vulva cell lines. These findings underscore the contribution of both genetic and epigenetic events to the underlying pathogenesis of squamous cell carcinoma of the vulva.

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Otolaryngology

Zhang, J., Z. Guan, V. Ramachandran, J. Dunford, M. Hoa, M. Edward, S. Ohnny, E. Michael, M. Edward, M. Seidman, K. Elisevich and S. Bowyer (2008). "Electrical modulation of tinnitus-related activity." Semin Hear **29**(4): 313-24.

[PDF Full-Text](#)

Department of Otolaryngology-Head and Neck Surgery & Neurology, Wayne State University School of Medicine, Henry Ford Health System, Detroit, Michigan

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Pathology

Lee, H., F. A. Meier, C. K. Ma, A. H. Ormsby and M. W. Lee (2008). "Eosinophilic globules in 3 cases of glomeruloid hemangioma of the head and neck: a characteristic offering more evidence for thanatosomes with or without POEMS." Am J Dermatopathol **30**(6): 539-44.

[PDF Full-Text](#)

Department of Pathology, Henry Ford Hospital, Detroit, MI 48202, USA. hlee1@hfhs.org

Glomeruloid hemangiomas (GHs) are glomeruli-like capillary tufts lined by endothelial cells that contain periodic acid-Schiff (PAS) positive eosinophilic globules (EGs). These hemangiomas are characteristic cutaneous manifestation of POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, and Skin changes). Hemangiomas histologically identical to GHs but not associated with POEMS have recently been designated as papillary hemangiomas. In this report, we present solitary head and neck GHs in 3 patients, 2 without POEMS, with particular attention to the characteristic EGs. We performed immunostains for hemoglobin A, kappa and lambda light chains, factor VIII-related antigen, CD31 and CD34, PAS stain after diastase digestion (PASD), and electron microscopic examinations on routinely fixed tissues containing EGs. Eosinophilic globules stained uniformly positive for PASD but only peripherally positive for hemoglobin and light chains on surfaces, with interiors negative for antigens. Factor VIII-related antigen and CD31 and CD34 confirmed cells containing EGs to be endothelial. Electron microscopic examination suggested that EGs are enlarged secondary lysosomes (thanatosomes). These features fail to support red blood cells or immunoglobulins as EG constituents. Glomeruloid hemangiomas may be vascular proliferations stimulated by endothelial cells' protein phagocytosis but not by phagocytosis of either hemoglobin-containing red blood cells or immunoglobulins. The vascular lesions in POEMS syndrome appear identical to papillary hemangioma in cases without the other syndromic manifestations.

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Pathology

Zikmund-Fisher, B. J., J. Brian, P. A. Ubel, D. M. Smith, H. A. Derry, J. B. McClure, A. Stark, R. K. Pitsch and A. Fagerlin (2008). "Communicating side effect risks in a tamoxifen prophylaxis decision aid: The debiasing influence of pictographs." Patient Education and Counseling **73**(2): 209-14.

[PDF Full-Text](#)

Henry Ford Health System, Detroit, Michigan

Objective: To experimentally test whether using pictographs (image matrices), incremental risk formats, and varied risk denominators would influence perceptions and comprehension of side effect risks in an online decision aid about Prophylactic use of tamoxifen to prevent primary breast cancers.

Methods: We recruited 631 women with elevated breast cancer risk from two healthcare organizations. Participants saw tailored estimates of the risks of 5 side effects: endometrial cancer, blood clotting, cataracts, hormonal symptoms, and sexual problems. Presentation format was randomly varied in a three factor design: (A) risk information was displayed either in Pictographs OF numeric text; (B) presentations either reported total risks with and without tamoxifen or highlighted the incremental risk most relevant for decision making; and (C) risk estimates used 100 or 1000 person denominators. Primary outcome measures included risk perceptions and gist knowledge.

Results: Incremental Risk formats consistently lowered perceived risk of side effects but resulted in low knowledge when displayed by numeric text only. Adding pictographs, however, produced significantly higher comprehension levels.

Conclusions: Pictographs make risk statistics easier to interpret, reducing biases associated with incremental risk presentations.

Practice implications: Including graphs in Risk communications is essential to Support in informed treatment decision-making process.

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Radiation Oncology

Barton, K. N., H. Stricker, S. L. Brown, M. Elshaikh, I. Aref, M. Lu, J. Pegg, Y. Zhang, K. C. Karvelis, F. Siddiqui, J. H. Kim, S. O. Freytag and B. Movsas (2008). "Phase I study of noninvasive imaging of adenovirus-mediated gene expression in the human prostate." Mol Ther **16**(10): 1761-9.

[Article Request Form](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, Michigan 48202, USA.

To monitor noninvasively potentially therapeutic adenoviruses for cancer, we have developed a methodology based on the sodium iodide symporter (NIS). Men with clinically localized prostate cancer were administered an intraprostatic injection of a replication-competent adenovirus, Ad5-yCD/utTK(SR39)rep-hNIS, armed with two suicide genes and the NIS gene. NIS gene expression (GE) was imaged noninvasively by uptake of Na(99m)TcO(4) in infected cells using single photon emission-computed tomography (SPECT). The investigational therapy was safe with 98% of the adverse events being grade 1 or 2. GE was detected in the prostate in seven of nine (78%) patients at 1×10^{12} virus particles (vp) but not at 1×10^{11} vp. Volume and total amount of GE was quantified by SPECT. Following injection of 1×10^{12} vp in 1 cm^3 , GE volume (GEV) increased to a mean of 6.6 cm^3 , representing, on average, 18% of the total prostate volume. GEV and intensity peaked 1-2 days after the adenovirus injection and was detectable in the prostate up to 7 days. Whole-body imaging demonstrated intraprostatic gene expression, and there was no evidence of extraprostatic dissemination of the adenovirus by SPECT imaging. The results demonstrate that noninvasive imaging of adenovirus-mediated gene therapy in humans is feasible and safe.

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Radiation Oncology

Kumar, S., A. Kolozsvary, R. Kohl, M. Lu, S. Brown and J. H. Kim (2008). "Radiation-induced skin injury in the animal model of scleroderma: implications for post-radiotherapy fibrosis." Radiat Oncol **3**: 40.

[PDF Full-Text](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI, USA.

skumar4@hfhs.org

BACKGROUND: Radiation therapy is generally contraindicated for cancer patients with collagen vascular diseases (CVD) such as scleroderma due to an increased risk of fibrosis. The tight skin (TSK) mouse has skin which, in some respects, mimics that of patients with scleroderma. The skin radiation response of TSK mice has not been previously reported. If TSK mice are shown to have radiation sensitive skin, they may prove to be a useful model to examine the mechanisms underlying skin radiation injury, protection, mitigation and treatment. **METHODS:** The hind limbs of TSK and parental control C57BL/6 mice received a radiation exposure sufficient to cause approximately the same level of acute injury. Endpoints included skin damage scored using a non-linear, semi-quantitative scale and tissue fibrosis assessed by measuring passive leg extension. In addition, TGF-beta1 cytokine levels were measured monthly in skin tissue. **RESULTS:** Contrary to our expectations, TSK mice were more resistant (i.e. 20%) to radiation than parental control mice. Although acute skin reactions were similar in both mouse strains, radiation injury in TSK mice continued to decrease with time such that several months after radiation there was significantly less skin damage and leg contraction compared to C57BL/6 mice ($p < 0.05$). Consistent with the expected association of transforming growth factor beta-1 (TGF-beta1) with late tissue injury, levels of the cytokine were significantly higher in the skin of the C57BL/6 mouse compared to TSK mouse at all time points ($p < 0.05$). **CONCLUSION:** TSK mice are not recommended as a model of scleroderma involving radiation injury. The genetic and molecular basis for reduced radiation injury observed in TSK mice warrants further investigation particularly to identify mechanisms capable of reducing tissue fibrosis after radiation injury.

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Radiation Oncology

Sarna, L., S. Swann, C. Langer, M. Werner-Wasik, N. Nicolaou, R. Komaki, M. Machtay, R. Byhardt, T. Wasserman and B. Movsas (2008). "Clinically meaningful differences in patient-reported outcomes with amifostine in combination with chemoradiation for locally advanced non-small-cell lung cancer: An analysis of RTOG 9801." Int J Rad Onc Biol Phys **72**(5): 1378-84.

[PDF Full-Text](#)

Henry Ford Health System, Detroit, Michigan

Purpose: The purpose of this study is to analyze changes in quality of life (QOL) and symptoms from pretreatment to 6 weeks posttreatment in a Phase III randomized study (Radiation Therapy Oncology Group 9801) of amifostine (AM) vs. no AM in patients with Stages II-III non-small-cell lung cancer receiving paclitaxel and carboplatin as induction and then concurrently with hyperfractionated radiation therapy (RT).

Methods and Materials: One hundred thirty-eight patients with baseline and 6-week posttreatment QOL data were analyzed. There were no significant differences in baseline demographics between those who did and did not have QOL data. The QOL and symptoms were assessed by using the European Organization for Research and Treatment of Cancer (EORTC) Global QOL and Pain subscales and the EORTC-Lung Cancer-13 symptom tool. Clinically relevant changes in QOL were characterized by 10-point differences in individual scores pre/post treatment. A daily diary of patient-rated difficulty swallowing and a weekly physician-rated dysphagia log (using National Cancer Institute Common Toxicity Criteria) were completed during treatment. Weight loss was monitored. Differences in outcomes were examined according to smoking status, alcohol use, and sex.

Results: Patients receiving AM reported significantly greater pain reduction after chemoradiation (34% vs. no AM, 21%), less difficulty swallowing during chemoradiation, and less weight loss than patients not receiving AM. However, physician-rated assessments of dysphagia were not significantly different by treatment arm. There were no other significant changes in QOL or symptoms according to treatment arm, smoking status, alcohol use, or sex.

Conclusions: Patient evaluations of difficulty swallowing and pain suggest benefits from AM use that are distinct from clinician-rated assessments.

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Radiation Oncology

Siddiqui, F., S. O. Freytag and B. Movsas (2008). "Hormones in addition to radiation for localized prostate cancer: How much and for whom?" Am J Hematol Oncol 7(10): 462-5.

[Article Request Form](#)

Department of Radiation Oncology, Henry Ford Health System, Detroit, MI

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Sleep Medicine

Richardson, G. and S. Wang-Weigand (2008). "Effects of long-term exposure to ramelteon, a melatonin receptor agonist, on endocrine function in adults with chronic insomnia." Hum Psychopharmacol **EPub Ahead of Print.**

[PDF Full-Text](#)

Henry Ford Hospital, Sleep Disorders and Research Center, Detroit, MI, USA.

OBJECTIVE: To evaluate the effects of ramelteon, an MT(1)/MT(2) melatonin receptor agonist used to treat insomnia, on endocrine function in adults with chronic insomnia. **METHODS:** This was a double-blind, placebo-controlled, trial of adults (18-45 years) with chronic insomnia. Subjects received either ramelteon 16 mg or placebo nightly for 6 months. Hormonal measures of the thyroid, reproductive, and adrenal axes were analyzed monthly and compared with baseline and placebo values. **RESULTS:** While isolated changes were detected at some time points, there were no consistent statistically significant differences between treatments on measures of thyroid function (total T4, free T4, TSH, and total T3), adrenal function (AM cortisol, and ACTH), or on most reproductive endocrine measures [LH, FSH, estradiol (women), total, and free testosterone (men)]. Prolactin concentrations were increased overall in women in the ramelteon group compared with placebo ($p = 0.003$). No clinical effects of elevated prolactin were reported; average menstrual cycle length, duration of menses, and ovulation probability did not differ between groups. **CONCLUSIONS:** Long-term

exposure to ramelteon 16 mg, a potent melatonin receptor agonist, resulted in mild, transient increase in prolactin, in women only, that were not associated with measurable reproductive effects. There were no consistent changes in other endocrine measures.

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Sleep Medicine

Roth, T. (2008). "Novel outcome measures of sleep, sleep loss and insomnia." Sleep Medicine **9**: S1-S2.

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Sleep Disorder and Research Center, Henry Ford Health System, 2799 West Grand Blvd, CEP-3-Detroit, MI 48202, USA

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Urology

Boris, R. S., A. Bhandari, L. S. Krane, D. Eun, S. Kaul and J. O. Peabody (2008). "Salvage robotic-assisted radical prostatectomy: initial results and early report of outcomes." BJU Int **Epub Ahead of Print**.

[PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Health System, Detroit, MI, USA.

OBJECTIVE To evaluate the initial results of salvage robotic-assisted radical prostatectomy (SRARP) after recurrence following primary radiotherapy (RT) for localized prostate cancer. **PATIENTS AND METHODS** Between December 2002 and January 2008, 11 patients had SRARP with pelvic lymph node dissection by one surgeon from one institution. Six patients had brachytherapy, three had external beam RT (EBRT), one intensity-modulated RT, and one received brachytherapy with an EBRT boost. All patients had prostate cancer on biopsy after RT, with negative computed tomography and bone scan. The mean (range) follow-up was 20.5 (1-77) months. **RESULTS** The mean interval from RT to SRARP was 53.2 months; the mean preoperative prostate-specific antigen (PSA) level was 5.2 ng/mL, the operative duration 183 min and the estimated blood loss 113 mL. One patient had prolonged lymphatic drainage, one had an anastomotic leak, and one had an anastomotic stricture requiring direct vision internal urethrotomy at 3 months. The mean duration of catheterization was 10.4 days and the hospital stay 1.4 days. Three patients had a biochemical recurrence, at 1, 2 and 43 months. In one of two patients with node-positive carcinoma of the prostate the PSA level failed to reach a nadir of zero after surgery. In patients with a minimum follow-up of 2 months, eight of 10 are continent (defined as zero to one pad per day) and two have erections adequate for intercourse with the use of phosphodiesterase-5 inhibitors. **CONCLUSION** SRARP after RT-resistant disease recurrence is feasible with minimal perioperative morbidity. Early functional outcomes appear to be at least equivalent with historical salvage RP series. Robotic extended pelvic lymph node dissection is safe and can improve the accuracy of surgical staging. A longer follow-up is necessary to better assess the functional and oncological outcomes.

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Urology

Chinnakannu, K., D. Chen, Y. Li, Z. Wang, Q. P. Dou, G. P. Reddy and F. H. Sarkar (2008). "Cell Cycle-Dependent Effects of 3,3'-Diindolylmethane on Proliferation and Apoptosis of Prostate Cancer Cells." J Cell Physiol **Epub Ahead of Print**.

[PDF Full-Text](#)

Vattikuti Urology Institute, Henry Ford Health System, Detroit, Michigan.

Epidemiological studies have shown that a diet rich in fruits and cruciferous vegetables is associated with a lower risk of prostate cancer. Indole-3-carbinol (I3C) and its dimeric product 3,3'-diindolylmethane (DIM) have been shown to exhibit anti-tumor activity both in vitro and in vivo. Recently, we have reported that a formulated

DIM (B-DIM) induced apoptosis and inhibited growth, angiogenesis, and invasion of prostate cancer cells by regulating Akt, NF-kappaB, VEGF and the androgen receptor (AR) signaling pathway. However, the precise molecular mechanism(s) by which B-DIM inhibits prostate cancer cell growth and induces apoptosis have not been fully elucidated. Most importantly, it is not known how B-DIM affects cell cycle regulators and proteasome activity, which are critically involved in cell growth and apoptosis. In this study, we investigated the effects of B-DIM on proteasome activity and AR transactivation with respect to B-DIM-mediated cell cycle regulation and induction of apoptosis in both androgen-sensitive LNCaP and androgen-insensitive C4-2B prostate cancer cells. We believe that our results show for the first time the cell cycle-dependent effects of B-DIM on proliferation and apoptosis of synchronized prostate cancer cells progressing from G(1) to S phase. B-DIM inhibited this progression by induction of p27(Kip1) and down-regulation of AR. We also show for the first time that B-DIM inhibits proteasome activity in S phase, leading to the inactivation of NF-kappaB signaling and induction of apoptosis in LNCaP and C4-2B cells. These results suggest that B-DIM could be a potent agent for the prevention and/or treatment of both hormone sensitive as well as hormone-refractory prostate cancer.

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Urology

Rogers, C. G., A. Metwalli, A. M. Blatt, G. Bratslavsky, M. Menon, W. M. Linehan and P. A. Pinto (2008). "Robotic partial nephrectomy for renal hilar tumors: a multi-institutional analysis." J Urol **180**(6): 2353-6; discussion 2356.

[PDF Full-Text](#)

Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA. Cr Rogers2@hfhs.org

PURPOSE: Laparoscopic partial nephrectomy is an advanced surgical procedure requiring technical skill in minimally invasive techniques. Tumors located adjacent to the renal hilum pose an additional challenge. We report a multi-institutional study of robotic partial nephrectomy for renal hilar tumors and describe our results. **MATERIALS AND METHODS:** We evaluated patients from 2 institutions who underwent robotic partial nephrectomy for renal hilar tumors. Renal hilar tumors were defined as tumors abutting the renal artery and/or renal vein on preoperative imaging. After clamping the renal hilar vessels tumors were excised with fine dissection from the renal vessels followed by sutured renal reconstruction. **RESULTS:** Robotic partial nephrectomy was successfully performed on 11 patients (mean age 56.4 years, range 30 to 76). Mean tumor size was 3.8 cm (range 2.3 to 6.4). Mean warm ischemia time was 28.9 minutes (range 20 to 39) and mean operating time was 202 minutes (range 154 to 253). Mean blood loss was 220 ml (range 50 to 750). Mean hospital stay was 2.6 days (range 1 to 4). Histopathological evaluation confirmed 8 cases of clear cell renal cell carcinoma, 1 of papillary renal cell carcinoma and 2 of chromophobe renal cell carcinoma. Surgical margins were negative for malignancy in all cases. **CONCLUSIONS:** Robotic partial nephrectomy is a safe and feasible approach for select patients with renal hilar tumors. Robotic assistance may facilitate tumor resection and renal reconstruction for challenging renal hilar tumors, offering a minimally invasive and nephron sparing surgical option for select patients who might otherwise require open surgery or total nephrectomy.

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