

Henry Ford Health System Publication List March 2009

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Biostatistics & Research Epidemiology

Johnson, C. C., C. L. M. Joseph, D. R. Ownby, S. L. Havstad, G. Wegienka and E. M. Zoratti (2009). "Exploring risk factors for food sensitization in a racially diverse birth cohort." J Allergy Clin Immunol **123**(2): S108. [Meeting Abstract](#)

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Biostatistics & Research Epidemiology

Joseph, C. L. M., D. R. Ownby, S. L. Havstad, G. R. Wegienka, E. M. Zoratti and C. C. Johnson (2009). "Supplemental foods and tolerance to peanut allergen by race." J Allergy Clin Immunol **123**(2): S108. [Meeting Abstract](#)

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Biostatistics & Research Epidemiology

Rossmann, M. D., R. Thompson, M. Frederick, M. C. Iannuzzi, B. A. Ryzhcki, J. P. Pandey, L. S. Newman, C. Rose, E. Magira and D. Monos (2008). "HLA and environmental interactions in sarcoidosis." Sarcoidosis Vasc Diffuse Lung Dis **25**(2): 125-32. [Article Request Form](#)

Sarcoidosis is a systemic granulomatosis of unknown etiology despite being described over 100 years ago. While both genetic predisposition and environmental exposures have been proposed as playing a role in this disease, there have not been any systematic investigations of gene-environmental interaction in this disease. In the ACCESS dataset, detailed environmental histories and high resolution HLA class II typing were performed on 476 cases of newly diagnosed sarcoidosis and 476 matched controls from the patients' community. We evaluated gene-environmental interactions in exposures or HLA class II alleles that were present in > 5% of the population and had an odd ratio of > 1.0. Four exposures and four HLA Class II alleles met these criteria and were evaluated. Significant interaction was observed between HLA DRB1*1101 and insecticide exposure at work ($p < 0.10$) and suggestive interaction was observed between HLA DRB1*1101 and exposure to mold and musty odors and D! RB1*1501 and insecticide exposure at work ($P < 0.15$). In addition, HLA DRB1*1101 and insecticide exposure at work was associated with extrapulmonary sarcoidosis, specifically cardiac sarcoidosis and hypercalcemia ($p < 0.05$) and HLA DRB1*1101 and exposure to molds and musty odors was associated with pulmonary only sarcoidosis ($P < 0.05$). These studies suggest that sarcoidosis is due to an interaction of genetic predisposition and environmental exposure in at least some cases of sarcoidosis. Future studies in defined

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8:30am-5:00pm F

phenotypes of sarcoidosis may be necessary to define environmental and genetic associations With sarcoidosis.

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Biostatistics & Research Epidemiology

Woodcroft, K. J., S. Havstad, K. R. Bobbitt, G. R. Wegienka, C. L. M. Joseph, E. M. Zoratti, D. R. Ownby and C. C. Johnson (2009). "Changes in intracellular IFN gamma and IL4 in the first year following pregnancy in WHEALS cohort mothers." J Allergy Clin Immunol **123**(2): S256. [Meeting Abstract](#)

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Biostatistics & Research Epidemiology

Wu, Q. J., Z. H. Wang, J. P. Kirkpatrick, Z. Chang, J. J. Meyer, M. Lu, C. Huntzinger and F. F. Yin (2009). "Impact of collimator leaf width and treatment technique on stereotactic radiosurgery and radiotherapy plans for intra- and extracranial lesions." Radiat Oncol **4**(3).

[PDF Full-Text](#)

Background: This study evaluated the dosimetric impact of various treatment techniques as well as collimator leaf width (2.5 vs 5 mm) for three groups of tumors - spine tumors, brain tumors abutting the brainstem, and liver tumors. These lesions often present challenges in maximizing dose to target volumes without exceeding critical organ tolerance. Specifically, this study evaluated the dosimetric benefits of various techniques and collimator leaf sizes as a function of lesion size and shape.

Methods: Fifteen cases (5 for each site) were studied retrospectively. All lesions either abutted or were an integral part of critical structures (brainstem, liver or spinal cord). For brain and liver lesions, treatment plans using a 3D-conformal static technique (3D), dynamic conformal arcs (DARC) or intensity modulation (IMRT) were designed with a conventional linear accelerator with standard 5 mm leaf width multi-leaf collimator, and a linear accelerator dedicated for radiosurgery and hypofractionated therapy with a 2.5 mm leaf width collimator. For the concave spine lesions, intensity modulation was required to provide adequate conformality; hence, only IMRT plans were evaluated using either the standard or small leaf-width collimators.

A total of 70 treatment plans were generated and each plan was individually optimized according to the technique employed. The Generalized Estimating Equation (GEE) was used to separate the impact of treatment technique from the MLC system on plan outcome, and t-tests were performed to evaluate statistical differences in target coverage and organ sparing between plans.

Results: The lesions ranged in size from 2.6 to 12.5 cc, 17.5 to 153 cc, and 20.9 to 87.7 cc for the brain, liver, and spine groups, respectively. As a group, brain lesions were smaller than spine and liver lesions. While brain and liver lesions were primarily ellipsoidal, spine lesions were more complex in shape, as they were all concave. Therefore, the brain and the liver groups were compared for volume effect, and the liver and spine groups were compared for shape. For the brain and liver groups, both the radiosurgery MLC and the IMRT technique contributed to the dose sparing of organs-at-risk(OARs), as dose in the high-dose regions of these OARs was reduced up to 15%, compared to the non-IMRT techniques employing a 5 mm leaf-width collimator. Also, the dose reduction contributed by the fine leaf-width MLC decreased, as dose savings at all levels diminished from 4 - 11% for the brain group to 1 - 5% for the liver group, as the target structures decreased in volume. The fine leaf-width collimator significantly improved spinal cord sparing, with dose reductions of 14 - 19% in high to middle dose regions, compared to the 5 mm leaf width collimator.

Conclusion: The fine leaf-width MLC in combination with the IMRT technique can yield dosimetric benefits in radiosurgery and hypofractionated radiotherapy. Treatment of small lesions in cases involving complex target/OAR geometry will especially benefit from use of a fine leaf-width MLC and the use of IMRT.

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Bone & Joint Center

Sethi, A., S. Lee and R. Vaidya (2009). "Transforaminal lumbar interbody fusion using unilateral pedicle screws and a translaminar screw." Eur Spine J **18**(3): 430-4. [PDF Full-Text](#)

Lumbar spinal fusion is advancing with minimally invasive techniques, bone graft alternatives, and new implants. This has resulted in significant reductions of operative time, duration of hospitalization, and higher success in fusion rates. However, costs have increased as many new technologies are expensive. This study was carried out to investigate the clinical outcomes and fusion rates of a low implant load construct of

unilateral pedicle screws and a translaminar screw in transforaminal lumbar interbody fusion (TLIF) which reduced the cost of the posterior implants by almost 50%. Nineteen consecutive patients who underwent single level TLIF with this construct were included in the study. Sixteen patients had a TLIF allograft interbody spacer placed, while in three a polyetheretherketone (PEEK) cage was used. Follow-up ranged from 15 to 54 months with a mean of 32 months. A clinical and radiographic evaluation was carried out preoperatively and at multiple time points following surgery. An overall improvement in Oswestry scores and visual analogue scales for leg and back pain (VAS) was observed. Three patients underwent revision surgery due to recurrence of back pain. All patients showed radiographic evidence of fusion from 9 to 26 months (mean 19) following surgery. This study suggests that unilateral pedicle screws and a contralateral translaminar screw are a cheaper and viable option for single level lumbar fusion.

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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 & Mineral Research Lab

Bishop, J. L., S. K. Kline, K. J. Alderink, R. Zauel and M. J. Bey (2009). "Glenoid inclination: In vivo measures in rotator cuff tear patients and associations with superior glenohumeral joint translation." J Shoulder Elbow Surg **18**(2): 231-6. [PDF Full-Text](#)

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 & Mineral Research Lab

Liu, F. X., Z. A. Zhu, Y. Q. Mao, M. Liu, T. T. Tang and S. J. Qiu (2009). "Inhibition of titanium particle-induced osteoclastogenesis through inactivation of NFATc1 by VIVIT peptide." *Biomaterials* **30**(9): 1756-62. [Article Request Form](#)

Osteoclastogenesis induced by particulate wear debris is a major pathological factor contributing to periprosthetic osteolysis. Although the nuclear factor of activated T cells c1 (NFATc1) is known to be involved in osteoclast differentiation, its effect on osteoclastogenesis in response to wear particles remains unclear. In the present study, we investigated the role of NFATc1 in the regulation of osteoclast differentiation from bone marrow macrophages (BMMs) stimulated with titanium (Ti) particles. The results showed that Ti particles could stimulate BMMs to produce proinflammatory cytokines (tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 beta, and IL-6) and differentiate into multinucleated osteoclasts in the presence of receptor activator of nuclear factor-kappa B ligand (RANKL). NFATc1 was expressed in BMMs and multinucleated cells cultured with Ti particles and RANKL. Inactivation of NFATc1 by 11R-VIVIT peptide potently impeded the Ti particle-induced osteoclastogenesis. 11R-VIVIT peptide does not have toxic effect on BMMs. Based on these data, we conclude that inactivation of NFATc1 by VIVIT peptide would provide a promising therapeutic target for the treatment of periprosthetic osteolysis.

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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. [Article Request Form](#)

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

Al-Mallah, M. H., K. Nasir, R. Katz, J. Takasu, S. S. Mao, J. Lima, J. J. Rivera, D. A. Blumke, W. G. Hundley, R. Blumenthal and M. J. Budoff (2009). "Correlation between left ventricular size by computed tomography and thoracic aortic distensibility measured by MRI: Multiethnic study of atherosclerosis (MESA) study." *J Am Coll Cardiol* **53**(10): A278.

[Meeting Abstract](#)

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Cardiology

Bhojraj, S. D. and M. H. Al-Mallah (2009). "Didactics and training in cardiovascular computed tomography angiography." *J Cardiovasc Comput Tomogr* **3**(1 Suppl): S57-63.

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Department of Cardiology, Henry Ford Hospital, 2799 W Grand Boulevard, Cardiology K-14, Detroit MI 48202, USA. sbhojra1@hfhs.org

As the role of cardiovascular computed tomography angiography (CCTA) is further expanded through research, the use of this technology will expand as a result of demand both from medical professionals and the public. To ensure a standardized quality of interpretation of these scans in the face of an increased demand for physicians qualified to interpret these studies, the Society of Cardiovascular Computed Tomography, along with several other professional societies, has proposed a didactic curriculum for the study of CCTA. This

review highlights the currently proposed didactic curriculum for the study of CCTA, examines current trends in training for both medical trainees and physicians in practice, and proposes future directions for the study of CCTA.

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Cardiology

Guerrero, M., S. Rastogi and H. N. Sabbab (2009). "Transformation of bone marrow stem cells into cardiomyocytes by tumor necrosis factor alpha." J Am Coll Cardiol **53**(10): A187.

[Meeting Abstract](#)

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Cardiology

Gupta, R. C., I. Ihsar, M. J. Wang, Jian, A. Zaretsky, M. S. Sabbah and H. N. Sabbab (2009). "Chronic therapy with vagus nerve stimulation is associated with reduced levels of circulating plasma biomarkers of heart failure." J Am Coll Cardiol **53**(10): A196. [Meeting](#)

[Abstract](#)

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Cardiology

Gupta, R. C. and H. N. Sabbab (2009). "Expression of microRNA-212 is increased in left ventricular myocardium of explanted failed human hearts and in dogs with experimentally-induced heart failure." J Am Coll Cardiol **53**(10): A146. [Meeting Abstract](#)

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Cardiology

Gupta, R. C. and H. N. Sabbab (2009). "Expression of H11 kinase is increased in left ventricular myocardium of explanted failed human hearts and in hearts of dogs with experimentally-induced heart failure." J Am Coll Cardiol **53**(10): A147. [Meeting Abstract](#)

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Cardiology

Gupta, R. C., M. J. Wang, I. Ihsar, A. Jiang, M. S. Sabbab and H. N. Sabbab (2009). "Comparisons of the acute effects of intra-aortic balloon counterpulsation therapy and continuous aortic flow therapy on plasma biomarkers in dogs with chronic heart failure." J Am Coll Cardiol **53**(10): A179-A180. [Article Request Form](#)

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Cardiology

Jaffery, Z., M. Hudson, S. Khanal, K. Ananthasubramaniam, H. Kim, A. Greenbaum, A. Kugelmass, G. Jacobsen and J. McCord (2009). "The recognition of acute coronary ischemia in the outpatient setting." J Thromb Thrombolysis **27**(1): 18-23. [PDF Full-Text](#)

Background The missed diagnosis of acute myocardial infarction has been studied in the Emergency Department, but few studies have investigated how often coronary ischemia is correctly identified in the outpatient setting. **Methods** This was a single center retrospective observational study of patients with Health Alliance Plan medical insurance hospitalized at a US tertiary center with acute myocardial infarction in 2004. Outpatient encounters in the 30 days preceding acute myocardial infarction were reviewed by two independent cardiologists for presenting symptoms and diagnostic decision-making in order to classify patient presentations as acute coronary ischemia, stable angina or neither. **Results** There were 331 patients with acute myocardial infarction, including 190 (57%) with a primary diagnosis of AMI and evaluated by a physician in the preceding 30 days. This group included 68 patients with 95 documented outpatient encounters by a primary care physician, cardiologist, or other internal medicine specialist which formed the final study population. Mean interval between these encounters and AMI was 17 +/- 11 days. Of these patients, 7 (10%) had symptoms of acute coronary ischemia, 5 (7%) had stable angina symptoms, and 56 (83%) had no symptoms of coronary

ischemia at their outpatient encounters. Of the 7 patients with acute coronary ischemic symptoms, 5 were correctly identified and 2 were misidentified. Conclusion A majority of patients with subsequent AMI visit an outpatient provider in the month preceding AMI. However, few present with symptoms of coronary ischemia in the outpatient setting (10%) and these symptoms are not always identified as such.

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Cardiology

Rastogi, S., V. G. Sharov, M. S. Sabbah and H. N. Sabbab (2009). "Intravenous injections of hypoxia-conditioned bone marrow-derived stem cell medium improve left ventricular function in dogs with heart failure." J Am Coll Cardiol **53**(10): A186. [Meeting Abstract](#)

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Cardiology

Sabbah, H. N. (2009). "Efficacy of the generation-2 acorn cardiac support device in dogs with chronic heart failure." J Heart Lung Transplant **28**(2): S102. [Meeting Abstract](#)

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Cardiology

Sabbah, H. N., S. Mishra, R. C. Gupta, S. Rastogi, B. Rousso and Y. Mika (2009). "Rapid in vitro and in vivo phosphorylation of phospholamban by cardiac contractility modulation electrical signals." J Am Coll Cardiol **53**(10): A191. [Meeting Abstract](#)

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Cardiology

Srivastava, A. V., B. Czerska, C. Williams, I. Alesh, L. Krese, M. A. Illuang, C. Drost, C. Smith, H. Nemeh, C. Tita, R. Brewer and D. Lanfear (2009). "High rates of false-positive hepatitis C antibody tests can occur after left ventricular assist device implantation." J Heart Lung Transplant **28**(2): S159-S160. [Meeting Abstract](#)

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Cardiology

Starling, R. C., M. Jessup, M. A. Acker, S. Boiling, J. K. Oh, D. L. Mann, H. N. Sabbab and S. H. Kubo (2009). "Mitral valve repair (MVR) in heart failure: 5 year follow-up from the MVR stratum of the Acorn Trial." J Heart Lung Transplant **28**(2): S313. [Meeting Abstract](#)

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Center for Health Services Research

Kind, P., J. E. Lafata, K. Matuszewski and D. Raisch (2009). "The use of QALYs in clinical and patient decision-making: Issues and prospects." Value in Health **12**(Suppl 1): S27-S30. [PDF Full-Text](#)

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Dermatology

Adams, B. and H. Kerr (2009). "A case of reactive angioendotheliomatosis." J Am Acad Dermatol **60**(3): AB45. [Meeting Abstract](#)

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Dermatology

Adams, B. and T. Shwayder (2008). "Steatocystoma multiplex suppurativum." Int J Dermatol **47**(11): 1155-6. [PDF Full-Text](#)

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

Chen, A. Y., M. Eide and T. Shwayder (2009). "Glomuvenous malformation in a boy with transposition of the great vessels: a case report and review of literature." *Pediatr Dermatol* **26**(1): 70-4. [PDF Full-Text](#)

Wright State University Boonshoft School of Medicine, Henry Ford Hospital, Detroit, MI 48202, USA.

We report a case of glomuvenous malformation (GVM) in an 11-year-old boy with a history of transposition of the great vessels. The glomulin gene was discovered in 1999, and multiple mutations have been identified with some of the mutations resulting in GVM. The molecular genetics, clinical presentation, histopathology, differential diagnosis, and management of GVM are reviewed. To our knowledge, no case of glomuvenous malformation in the setting of transposition of the great vessels has ever been reported in the literature.

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Dermatology

Cook-Bolden, F., D. Chen, L. Eichenfield and L. Stein-Gold (2009). "Managing moderate to severe acne in adolescents: Benefits of a fixed combination clindamycin phosphate (1.2%) and low concentration benzoyl peroxide (2.5%) aqueous gel in a subpopulation of 1755 subjects." *J Am Acad Dermatol* **60**(3): AB22. [Meeting Abstract](#)

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Dermatology

Elrashidy, D. and H. A. Kerr (2009). "Contact dermatitis to vascular tape used for fluoroscopy: A case report." *J Am Acad Dermatol* **60**(3): AB72. [Meeting Abstract](#)

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Dermatology

Gathers, R. C., M. Jankowski, M. Eide and H. W. Lim (2009). "Hair grooming practices and central centrifugal cicatricial alopecia." *J Am Acad Dermatol* **60**(4): 574-8. [PDF Full-Text](#)

Multicultural Dermatology Center, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan 48202, USA. rgather1@hfhs.org

BACKGROUND: The cause of central centrifugal cicatricial alopecia (CCCA) in African American women remains to be elucidated. **OBJECTIVE:** This study was designed to determine the hair-grooming practices in African American women with and without CCCA and to evaluate possible etiologic factors. **METHODS:** Utilizing a novel survey instrument, the Hair Grooming Assessment Survey, we performed a retrospective comparative survey of the hair-grooming practices of two populations of African American women seen and evaluated at the Department of Dermatology, Henry Ford Hospital in Detroit, MI, between 2000 and 2007. The case group were women with clinical and histologic diagnosis of CCCA, and the control group were those without a history of alopecia. **RESULTS:** All 101 surveys that were returned were analyzed (51 from the case group and 50 from the control group). A strong association was found between the use of both sewn-in hair weaving and cornrow or braided hairstyles with artificial hair extensions and CCCA ($P < .04$, $P < .03$, respectively). Similarly, women with CCCA were more likely to report a history of "damage", typically defined as uncomfortable pulling and tenderness, from both sewn-in and glued-in weaves, and from cornrow or braided hairstyles with artificial hair extensions ($P < .001$, $P < .02$, and $P < .03$, respectively). In contrast to previous anecdotal beliefs, no correlation was found between the use of either hot combing or hair relaxers and the development of CCCA. **LIMITATIONS:** Results are limited by patient recall of past hair grooming practices. Also, as hair grooming practices may vary by geographic region, these results may not be generalized to all women of African descent. **CONCLUSION:** There is a clear difference in both quantitative and qualitative hair grooming practices among African American women with CCCA.

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Dermatology

Gathers, R. C. and H. W. Lim (2009). "Central centrifugal cicatricial alopecia: past, present, and future." J Am Acad Dermatol **60**(4): 660-8. [PDF Full-Text](#)

Multicultural Dermatology Center, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan 48202, USA. rgather1@hfhs.org

Clinical scarring alopecia in African American women has been recognized for years. The classification of this unique form of alopecia dates back to Lopresti, who first described the entity called "hot comb alopecia." More recently, the term "central centrifugal cicatricial alopecia" has been adopted to describe a progressive vertex-centered alopecia most common in women of African descent. While this form of hair loss is widely recognized, and may even be on the rise, the causes of central centrifugal cicatricial alopecia are a constant source of debate and remain to be elucidated. This review outlines the descriptive evolution of central centrifugal cicatricial alopecia and the historical controversies ascribed to its pathoetiology; it also examines African hair structure and discusses how hair structure along with common physical and chemical implements utilized by individuals with African hair type may play a causal role in the development of central centrifugal cicatricial alopecia.

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Dermatology

Ghaferi, J. and T. Shwayder (2009). "Two new cases of epidermolysis bullosa simplex with mottled pigmentation: A father and son." J Am Acad Dermatol **60**(3): AB96. [Meeting Abstract](#)

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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 (2009). "A clinical trial and molecular study of photoadaptation in vitiligo." Br J Dermatol **160**(3): 534-9. [PDF Full-Text](#)

Photoadaptation to ultraviolet (UV) B phototherapy is due to both pigmentary and nonpigmentary influences. To measure photoadaptation in vitiliginous skin and to compare it with normal pigmented skin. 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.

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).

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

Keimig, E. (Jackson, D.). "Psoriatic eruption after placement of a red tattoo: A case report and review of the literature." J Am Acad Dermatol **60**(3): AB46. [Meeting Abstract](#)

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Dermatology

Klekowski, N. and T. Shwayder (2009). "Painless hand nodules in a 15-year-old boy." Pediatr Dermatol **26**(1): 91-2. [PDF Full-Text](#)

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Dermatology

Kohen, L. and H. Kerr (2009). "Alopecia neoplastica." J Am Acad Dermatol **60**(3): AB42. [Meeting Abstract](#)

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Dermatology

Liggett, J. and D. Ozog (2009). "Cutaneous cryptococcus in a renal transplant patient with mental status change: A case report and review of the literature." J Am Acad Dermatol **60**(3): AB116. [Meeting Abstract](#)

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Dermatology

Mahmoud, B., C. Hexsel, H. Lim and I. Hamzavi (2009). "Effects of long wavelength ultraviolet A and visible light on dark skin." J Am Acad Dermatol **60**(3): AB1. [Meeting Abstract](#)

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Dermatology

Mahmoud, B., C. Hexsel, D. Ozog, E. Tierney and I. Hamzavi (2009). "Clinical and histopathologic evaluation of hidradenitis suppurativa treated with long-pulsed nd:YAG laser." J Am Acad Dermatol **60**(3): AB192. [Meeting Abstract](#)

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Dermatology

Mahmoud, B., D. Marcus and I. Hamzavi (2009). "Granuloma annulare treated with rifampin, ofloxacin, and minocycline." J Am Acad Dermatol **60**(3): AB49. [Meeting Abstract](#)

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Dermatology

Parker, J. and I. Hamzavi (2009). "Q-switched Nd:YAG 1064-nm laser for the treatment of acne-induced postinflammatory hyperpigmentation." J Am Acad Dermatol **60**(3): AB198. [Meeting Abstract](#)

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Dermatology

Rondina, A. and R. C. Gathers (2009). "A case of central centrifugal cicatricial alopecia in an African American man." J Am Acad Dermatol **60**(3): AB102. [Meeting Abstract](#)

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Dermatology

Srivastava, D., H. Lim and H. Kerr (2009). "A case of alternariosis in a renal transplant patient." J Am Acad Dermatol **60**(3): AB115. [Meeting Abstract](#)

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Dermatology

Srivastava, D., B. Mahmoud, D. Ozog, H. Lim and J. Janiga (2009). "The safety and efficacy of fractional laser treatments for acne scars in Fitzpatrick skin types IV to VI." J Am Acad Dermatol **60**(3): AB197. [Meeting Abstract](#)

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Dermatology

Wenker, T. and H. Wong (2009). "Paraneoplastic pemphigus associated with melanoma." J Am Acad Dermatol **60**(3): AB106. [Meeting Abstract](#)

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Dermatology

Wolf, E. K. and T. Shwayder (2009). "Nijmegen breakage syndrome associated with porokeratosis." Pediatr Dermatol **26**(1): 106-8. [PDF Full-Text](#)

Nijmegen breakage syndrome (NBS) is a rare DNA repair disorder caused by mutations in the NBS-1 gene (8q21). Patients with this autosomal recessive condition have characteristic facial features, microcephaly present at birth, immunodeficiency, predisposition to malignancy, ionizing radiation hypersensitivity, and growth retardation. We report a 12-year-old boy with NBS associated with porokeratosis; to our knowledge this association has not previously been reported.

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Dermatology

Woo, D. and T. Shwayder (2009). "A rare case of multiple pigmented eccrine hidrocystomas within scars in a patient with recessive dystrophic epidermolysis bullosa." J Am Acad Dermatol **60**(3): AB78. [Meeting Abstract](#)

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Dermatology

Wright, D. R., I. J. Frieden, S. J. Orlow, H. T. Shin, S. Chamlin, J. V. Schaffer and A. S. Paller (2009). "The misnomer "macrocephaly-cutis marmorata telangiectatica congenita syndrome": report of 12 new cases and support for revising the name to macrocephaly-capillary malformations." Arch Dermatol **145**(3): 287-93. [PDF Full-Text](#)

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

BACKGROUND: The condition known as macrocephaly-cutis marmorata telangiectatica congenita syndrome (M-CMTC) is a rare congenital syndrome of unknown etiology characterized by macrocephaly and vascular lesions that have been described as either cutis marmorata or cutis marmorata telangiectatica congenita (CMTC). Most patients also exhibit facial and limb asymmetry; somatic overgrowth; developmental delay; capillary malformations of the nose, philtrum, and/or upper lip; neurologic abnormalities; syndactyly or polydactyly; craniofacial abnormalities; and joint laxity or soft skin. **OBSERVATIONS:** We describe 12 patients with this condition from tertiary care medical centers (8 cases) and accrued via an M-CMTC support group Web site (4 cases). All patients showed reticulated or confluent port-wine stains (PWS), not CMTC. Seven of the 12 patients also had centrofacial capillary malformations. In our comprehensive review of 100 previously reported cases, only 34 were accompanied by photographs that were sufficiently clear to review for diagnostic purposes. None had true CMTC, with most having reticulated PWS or persistent cutis marmorata.

CONCLUSIONS: Reticulated or confluent PWS and persistent capillary malformations of the central face, rather than CMTC, are the most characteristic cutaneous vascular anomalies seen in so-called M-CMTC syndrome. The name macrocephaly-capillary malformations (M-CM) more accurately reflects the features of this syndrome.

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Dermatology

Wright, D. R., D. Haggins, M. Caffins and M. Lokitz (2009). "Eosinophilic fasciitis versus morphea profunda. A spectrum of deep morphea." J Am Acad Dermatol **60**(3): AB66.

[Meeting Abstract](#)

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Dermatology

Xu, L. and H. Kerr (2009). "Ulcerative sarcoidosis: A case report." J Am Acad Dermatol **60**(3): AB126. [Meeting Abstract](#)

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Diagnostic Radiology

Arbab, A. S., B. Janic, J. Haller, E. Pawelczyk, W. Liu and J. A. Frank (2009). "In vivo cellular imaging for translational medical research." Current Medical Imaging Reviews **5**(1): 19-38. [Article Request Form](#)

Personalized treatment using stem, modified or genetically engineered, cells is becoming a reality in the field of medicine, in which allogenic or autologous cells can be used for treatment and possibly for early diagnosis of diseases. Hematopoietic, stromal and organ specific stem cells are under evaluation for cell-based therapies for cardiac, neurological, autoimmune and other disorders. Cytotoxic or genetically altered T-cells are under clinical trial for the treatment of hematopoietic or other malignant diseases. Before using stem cells in clinical trials, translational research in experimental animal models are essential, with a critical emphasis on developing noninvasive methods for tracking the temporal and spatial homing of these cells to target tissues. Moreover, it is necessary to determine the transplanted cells, engraftment efficiency and functional capability. Various in vivo imaging modalities are in use to track the movement and incorporation of administered cells. Tagging cells with reporter genes, fluorescent dyes or different contrast agents transforms them into cellular probes or imaging agents. Recent reports have shown that magnetically labeled cells can be used as cellular magnetic resonance imaging (MRI) probes, demonstrating the cell trafficking to target tissues. In this review, we will discuss the methods to transform cells into probes for in vivo imaging, along with their advantages and disadvantages as well as the future clinical applicability of cellular imaging method and corresponding imaging modality.

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Diagnostic Radiology

Hamidian, H., H. Soltanian-Zadeh, R. Faraji-Dana and M. Gity (2009). "Estimating brain deformation during surgery using finite element method: Optimization and comparison of two linear models." Journal of Signal Processing Systems for Signal Image and Video Technology **55**(1-3): 157-67. [Article Request Form](#)

This paper addresses estimation of brain deformation during craniotomy using finite element modeling. Two mechanical models are optimized and compared for this purpose: linear solid-mechanic model and linear elastic model. Both models assume the realistic finite deformation of the brain after opening the skull. In this study, we use pre-operative and intra-operative magnetic resonance images (MRI) of five patients undergoing brain tumor surgery. Anatomical landmarks are identified by an expert radiologist on MRI and used for the method development and comparison studies. We use tetrahedral finite element meshes and optimize model parameters by minimizing the mean distance between the predicted locations of the anatomical landmarks using the pre-operative images and their actual locations on the intra-operative images. Evaluation of the objective function using a second set of landmarks not used in the optimization process suggests that accuracy of the solid mechanic model is higher than that of the elastic model for our application. Visual inspection of the results confirms this conclusion. The proposed method along with the location information of the surface landmarks measured in the operating room and marked on the pre-operative images can be used to estimate the brain deformations without needing intra-operative images. In this case, since the parameters of the brain tissue are not the same for different patients, the proposed optimization process is crucial for obtaining accurate results.

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Emergency Medicine

Kanjanauthai, S., T. Kanluen and M. Bergman (2009). "Tension chylothorax: A rare life threatening entity after pneumonectomy." Heart Lung Circ **18**(1): 55-6. [Article Request Form](#)

Chylothorax is an accumulation of chyle in the pleural space due to disruption or blockage of the thoracic duct or its lymphatic tributaries. The thoracic duct carries chyle, which is defined as lymphatic fluid of intestinal origin, to the bloodstream. Chylothorax can occur due to traumatic or non-traumatic etiologies. Chylothorax is a known complication of thoracic surgery and can occur after significant trauma. However, tension chylothorax is an extremely rare and life threatening complication after thoracic surgery. We describe a patient who developed tension chylothorax 2 weeks after a left pneumonectomy was performed. Early recognition and prompt treatment of this life threatening entity are essential.

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Emergency Medicine

Rivers, E. P., V. Coba, A. Visbal, M. Whitmill and D. Amponsah (2008). "Management of sepsis: early resuscitation." Clin Chest Med **29**(4): 689-704, ix-x. [Article Request Form](#)

Department of Emergency Medicine, Henry Ford Health Systems, 270-Clara Ford Pavilion, 2799 West Grand Boulevard, Detroit, MI 48202, USA. erivers1@hfhs.org

Key links in the chain of survival for the management of severe sepsis and septic shock are early identification and comprehensive resuscitation of high-risk patients. Multiple studies have shown that the first 6 hours of early sepsis management are especially important from a diagnostic, pathogenic, and therapeutic perspective, and that steps taken during this period can have a significant impact on outcome. The recognition of this critical time period and the robust outcome benefit realized in previous studies provides the rationale for adopting early resuscitation as a distinct intervention. Sepsis joins trauma, stroke, and acute myocardial infarction in having "golden hours," representing a critical opportunity early on in the course of disease for actions that offer the most benefit.

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Gastroenterology

Castillo, E., S. Pelletier, S. Kumer, M. Abouljoud, G. Divine and D. Moonka (2009).

"Incidental hepatocellular carcinoma after liver transplantation: population characteristics and outcomes." Transplant Proc **41**(1): 219-21. [PDF Full-Text](#)

Division of Gastroenterology, Henry Ford Health System, Detroit, Michigan 48322, USA.

We combined data from two liver transplant centers to determine the tumor characteristics and outcomes of 51 patients transplanted with incidental hepatocellular carcinoma (iHCC) compared with 143 patients transplanted for previously known HCC (pkHCC). There were no differences in age, gender, or frequency of hepatitis C infection. Patients with iHCC were more likely to be African-American (22% vs 10%; $P = .016$), more likely to be screened by ultrasound (38% vs 9%; $P < .001$), had a lower alpha-fetoprotein (83.9 +/- 258.1 vs 572.4 +/- 2376.4 ng/mL; $P = .005$), and had a higher model for end-stage liver disease (MELD) score (14.3 +/- 4.1 vs 11.8 +/- 4.7; $P < .001$). The liver explants of patients with iHCC had smaller total tumor burden than patients with pkHCC (3.1 +/- 3.5 vs 4.1 +/- 2.6 cm; $P < .001$), but a similar percentage of single lesions (66% vs 65%) and tumors that met Milan criteria (76% vs 65%). Patients with iHCC had 1-, 3-, and 5-year survivals of 78%, 67%, and 58%, and 1-, 3-, and 5-year recurrence-free survivals of 90%, 87%, and 87% compared with the 1-, 3-, and 5-year survivals of 90%, 82%, and 70%, and the 1-, 3-, and 5-year tumor-free survivals of 91%, 84%, and 78% in patients with pkHCC. We concluded that patients with iHCC were more likely to be African-American, to be screened by ultrasound, to have a lower alpha-fetoprotein, and a higher MELD score. Ultrasound is not a sensitive modality for screening patients for HCC. Patients with iHCC do not have an advantage in survival over those with pkHCC.

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Gastroenterology

Krishnan, P. V., Z. Z. Feng and S. C. Gordon (2009). "Prolonged Intrahepatic Cholestasis and Renal Failure Secondary to Anabolic Androgenic Steroid-Enriched Dietary

Supplements." [J Clin Gastroenterol](#). EPub Ahead of Print. [Article Request Form](#) *Sladen Library has an electronic subscription to this title, but the article was not available at the time of this publication.*

Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI.

The illegal enrichment of anabolic androgenic steroids in over-the-counter dietary supplements is well documented, but the health consequences have not been widely recognized. Three recent reports document cholestatic jaundice and nephropathy due to these compounds. We present 3 additional cases of anabolic androgenic steroid-enriched dietary supplement-induced hepatotoxicity and 1 case of renal failure, and we review the literature and the relevant features of this growing health concern. Recognition of this entity could obviate the need for invasive diagnostic testing and hospitalization and facilitate diagnosis and appropriate counseling.

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Gastroenterology

Moonka, D., E. Castillo, S. Kumer, M. Abouljoud, G. Divine and S. Pelletier (2009). "Impact of model for end-stage liver disease on patient survival and disease-free survival in patients receiving liver transplantation for hepatocellular carcinoma." [Transplant Proc](#) **41**(1): 216-8.

[PDF Full-Text](#)

Division of Gastroenterology, Henry Ford Health System, Detroit, Michigan 48322, USA.

dmoonkal@hfhs.org

We combined data from two transplant centers to determine the impact of the model for end-stage liver disease (MELD) allocation system on outcomes in patients undergoing liver transplantation for hepatocellular carcinoma (HCC). We compared 55 patients listed before MELD to 117 patients in the MELD era. Patients before MELD were less likely to receive a transplant (67% vs 91%) and waited a median of 127 days vs 20 days ($P < .001$). On an intention to treat (ITT) basis, the 1-, 3-, and 5-year survivals for patients before MELD were 79%, 60%, and 48%, and in the MELD era were 84%, 73%, and 73% ($P = .055$). On an ITT basis, the 1-, 3-, and 5-year tumor-free survivals before MELD were 58%, 58%, and 55% vs 83%, 74%, and 70% in the MELD era ($P = .018$). In patients who received a transplant, however, there were no differences in overall or tumor-free survival. In these patients, the 1-, 3-, and 5-year patient survivals were 92%, 84%, and 67% before MELD, and 90%, 81%, and 81% in the MELD era ($P = .57$). In transplanted patients, the 1-, 3-, and 5-year tumor-free survivals before MELD were 88%, 88%, and 83% vs 92%, 83%, and 78% in the MELD era ($P = .403$). On explant, patients listed before MELD had lower grade tumors ($P = .046$). We concluded that patients with HCC listed in the MELD era had higher and more rapid rates of transplantation with improvements in survival. However, the more efficacious rates of transplantation did not result in lower rates of tumor recurrence.

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Brell, J. M., S. S. Krishnamurthi, M. Javle, J. Saltzman, I. Wollner, R. Pelley, A. Dowlati, B. N. Kantharaj, M. D. Schluchter, L. Rath, S. P. Ivy and S. C. Remick (2009). "A multi-center phase II study of oxaliplatin, irinotecan, and capecitabine in advanced gastric/gastroesophageal junction carcinoma." [Cancer Chemother Pharmacol](#) **63**(5): 851-7.

[PDF Full-Text](#)

There is no standard first-line therapy for advanced gastric and gastroesophageal junction (GEJ) adenocarcinoma and the prognosis remains poor. Our institution conducted a phase I study of oxaliplatin, irinotecan, and capecitabine given in a novel, weekly schedule. The regimen was tolerated; pharmacodynamic studies revealed no drug interactions, and there was one confirmed response in a gastric cancer patient. We performed a phase II trial in advanced gastric and GEJ adenocarcinoma to determine response rate and response duration.

This was a multi-center single treatment arm study involving six sites. Only prior adjuvant therapy was allowed. Patients had ECOG performance status of 0-2, adequate organ function, and were able to tolerate oral medications. All patients received oxaliplatin 60 mg/m² intravenously (IV) and irinotecan 50 mg/m² IV

weekly times 4 weeks with a 2-week rest period. Capecitabine 450 mg bid orally was received on days 1 through 5 every week for 4 weeks, followed by a 2-week rest. Patients were assessed for response after the first two cycles; response duration, overall survival, and adverse events were also recorded. We estimated an improvement in historical response rate by 30% would have clinical meaning. A total of 39 patients were accrued and all were assessed for toxicity; 30 patients were evaluable for response. The median age was 57.8 years (31-79 years) and 74% were male. Two patients had a complete response, with nine patients achieving a partial response. The total response rate was 28%, with nine patients not evaluable for response. The median response duration was noted at 5.97 months and median overall survival was 8.98 months. There were no grade 5 treatment related events, with all deaths secondary to disease progression. Only five grade 4 events occurred (neutropenia, hyperkalemia, hypokalemia (2), thrombosis/embolism) without grade 4 diarrhea or sensory neuropathy. Oxaliplatin, irinotecan, and capecitabine given in a novel, weekly schedule does induce responses in advanced gastric and GEJ adenocarcinoma. However, the total response rate is modest and not an improvement over other regimens.

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Dabak, V. and P. Kuriakose (2009). "Thalidomide-induced severe hepatotoxicity." Cancer Chemother Pharmacol **63**(4): 583-5. [PDF Full-Text](#)

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Dabak, V. S., E. U. Duran, M. Dawood and A. Hanbali (2008). "Metastatic bone survey in monoclonal gammopathy of undertermined significance: Useful for not?" Blood **112**(11): 942-3. [PDF Full-Text](#)

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Hanbali, A. and Y. Khaled (2009). "Incidence of hepatitis B reactivation following Rituximab therapy." Am J Hematol **84**(3): 195. [PDF Full-Text](#)

Division of Hematology/Oncology, Department of Medicine, Henry Ford Hospital, Detroit, MI, USA.

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Hematology, Medical Oncology & Josephine Ford Cancer Center

Vega, J., M. Younes and P. Kuriakose (2008). "The significance of unexplained macrocytosis." Blood **112**(11): 1183-4. [PDF Full-Text](#)

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Hospitalist Medicine

Alesh, I., A. V. Srivastava, D. Lanfear, C. Williams, H. Nemeh, F. Matta, C. Tita, R. Brewer, C. Smith and B. Czerska (2009). "The effect of the patient's medical insurance on post cardiac transplant outcomes: A single center experience." J Heart Lung Transplant **28**(2): S271. [PDF Full-Text](#)

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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. PMC2615526. [PDF Full-Text](#)

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

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 Ser1177. 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 Ser473 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 Ser1177 by 89 +/- 24% ($p < 0.01$; $n = 7$) but had no effect on Ser633. 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 Ser1177. This enhances NO production and inhibits sodium transport.

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Hypertension & Vascular Research

Hong, N. J. and J. L. Garvin (2009). "Nitric oxide reduces flow-induced superoxide production via cGMP-dependent protein kinase in thick ascending limbs." [Am J Physiol Renal Physiol](#). Epub Ahead of Print. [PDF Full-Text](#)

Henry Ford Hospital.

We have shown that increased renal tubular flow induces O₂(-) and NO production in thick ascending limbs (TAL). However, the interaction of flow-stimulated NO and O₂(-) in TALs is unclear. We hypothesized that NO inhibits flow-induced O₂(-) production in TALs via cGMP-dependent protein kinase (PKG). We measured flow-stimulated O₂(-) production in rat TALs using dihydroethidium in the absence and presence of L-arginine (0.3 mM), the substrate for NO synthase. Addition of L-arginine reduced flow-induced net O₂(-) production from 68 +/- to 17 +/- 4 AU/s ($p < 0.002$). Addition of the NO synthase inhibitor L-NAME (5 mM) in the presence of L-arginine stimulated production (L-arginine: 15 +/- 4 AU/s vs. L-arginine + L-NAME: 63 +/- 7 AU/s; $p < 0.002$). The guanylate cyclase inhibitor LY-83583 (10 microM) also enhanced flow-induced net O₂(-) production in the presence of L-arginine (L-arginine: 7 +/- 4 AU/s vs. L-arginine + LY-83583: 53 +/- 7 AU/s; $p < 0.01$). In the presence of LY-83583, L-arginine only reduced flow-induced net O₂(-) by 36% (LY-83583: 80 +/- 7 AU/s vs. LY-83583 + L-arginine: 51 +/- 3 AU/s; $p < 0.006$). The cGMP analog dibutyryl (db)-cGMP reduced flow-induced net O₂(-) from 39 +/- 9 to 7 +/- 3 AU/s ($p < 0.03$). The PKG inhibitor KT-5823 (5 microM) partially restored flow-induced net O₂(-) in the presence of L-arginine (L-arginine: 4 +/- 4 AU/s vs. L-arginine + KT-5823: 32 +/- 9 AU/s; $p < 0.03$) and db-cGMP (db-cGMP: 9 +/- 7 AU/s vs. db-cGMP + KT-5823: 54 +/- 5 AU/s; $p < 0.01$). Phosphodiesterase II inhibition had no effect on arginine-inhibited O₂(-) production. We conclude that: 1) NO reduces flow-stimulated O₂(-) production; 2) this occurs primarily via the cGMP/PKG pathway; and 3) O₂(-) scavenging by NO plays a minor role. Key words: Reactive oxygen species, soluble guanylate cyclase, cGMP-dependent protein kinase, phosphodiesterase.

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Hypertension & Vascular Research

Liu, Y. H., M. D'Ambrosio, T. D. Liao, H. Peng, N. E. Rhaleb, U. Sharma, S. Andre, H. J. Gabius and O. A. Carretero (2009). "N-acetyl-seryl-aspartyl-lysyl-proline prevents cardiac remodeling and dysfunction induced by galectin-3, a mammalian adhesion/growth-regulatory lectin." [Am J Physiol Heart Circ Physiol](#) **296**(2): H404-12. PMC2643891. [PDF Full-Text](#)

Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.

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

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Hypertension & Vascular Research

Mendez, M. (2009). "CBP/p300 in renin homeostasis: Can they drive the fate?" Am J Physiol Heart Circ Physiol. EPub Ahead of Print. [PDF Full-Text](#)

Henry Ford Hospital.

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Internal Medicine

Habib, Z. A., L. Tzogias, S. L. Havstad, K. Wells, G. Divine, D. E. Lanfear, J. Tang, R. Krajenta, M. Pladevall and L. K. Williams (2009). "Relationship between thiazolidinedione use and cardiovascular outcomes and all-cause mortality among patients with diabetes: a time-updated propensity analysis." Pharmacoepidemiol Drug Saf. EPub Ahead of Print. [Article Request Form](#)

Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA.

PURPOSE: To investigate the association of the thiazolidinediones (TZDs), rosiglitazone, and pioglitazone, together and individually on the risk of cardiovascular outcomes and all-cause mortality, using time-updated propensity score adjusted analysis. **METHODS:** We conducted a retrospective cohort study in a large vertically integrated health system in southeast Michigan. Cohort inclusion criteria included adult patients with diabetes treated with oral medications and followed longitudinally within the health system between 1 January 2000 and 1 December 2006. The primary outcome was fatal and non-fatal acute myocardial infarction (AMI). Secondary outcomes included hospitalizations for congestive heart failure (CHF), fatal, and non-fatal cerebrovascular accidents (CVA) and transient ischemic attacks (TIA), combined coronary heart disease (CHD) events, and all-cause mortality. **RESULTS:** 19 171 patients were included in this study. Use of TZDs (adjusted hazard ratio (aHR) with propensity adjustment (PA), 0.92; 95% confidence interval (CI) 0.73-1.17), rosiglitazone (aHR with PA, 1.06; 95%CI 0.66-1.70), and pioglitazone (aHR with PA, 0.91; 95%CI 0.69-1.21) was not associated with a higher risk of AMI. However, pioglitazone use was associated with a reduction in all-cause mortality (aHR with PA, 0.60; 95%CI 0.42-0.96). Compared with rosiglitazone, pioglitazone use was associated with a lower risk of all outcomes assessed, particularly CHF (p = 0.013) and combined CHD events (p = 0.048). **CONCLUSIONS:** Our findings suggest that pioglitazone may have a more favorable risk profile when compared to rosiglitazone, arguing against a singular effect for TZDs on cardiovascular outcomes.

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Medical Genetics

Adeyinka, A., S. Wei, C. Abbud-Mendez, J. Sanchez and M. W. Lee (2009). "Homozygous structural rearrangement 16p13: a mechanism of tumorigenesis in sporadic renal angiomyolipoma?" Am J Med Genet A **149A**(4): 809-11. [PDF Full-Text](#)

Department of Medical Genetics, Henry Ford Health System, Detroit, Michigan 48202, USA.
aadeyin1@hfhs.org

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Nephrology

Besarab, A., S. Frinak and J. Yee (2009). "What is so bad about a hemoglobin level of 12 to 13 g/dL for chronic kidney disease patients anyway?" Adv Chronic Kidney Dis **16**(2): 131-42. [PDF Full-Text](#)

Division of Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI 48202-2699, USA. abesara1@hfhs.org

Randomized controlled trials (RCTs) clearly indicate a possible cardiovascular morbidity and mortality risk when deliberately targeting a normal hemoglobin (Hb) concentration of 13 to 15 g/dL. By contrast, observational studies point to greater hospitalization and mortality at Hb levels <11 g/dL. There are no direct data to help us determine where, within this broad range, the optimal Hb lies. In RCTs and observational studies, significant confounding from the interrelationships of anemia and epoetin resistance occurs in patients with a serious illness. Patients with comorbidities such as malnutrition and inflammatory processes are more resistant to epoetin and, invariably, require greater cumulative epoetin doses. The effect of a higher erythropoiesis-stimulating agent (ESA) dose on increasing mortality has been noted repeatedly in post hoc analyses of RCTs. It is therefore too simplistic to solely attribute the outcomes achieved in RCTs to "target Hb." We discuss various mechanisms for potential harm at higher Hb levels as opposed to those that may be obtained from higher epoetin doses. For the individual patient, the therapeutic decision should center on what Hb is most appropriate at a "safe" ESA dose. Consequently, an Hb of 12 to 13 g/dL may be totally appropriate in some patient populations.

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Nephrology

Fehmi, H., Y. Osman, S. Bhat, K. Nguyen, O. Daramola, T. Cantor, M. C. Monier-Faugere, J. Yee and H. H. Malluche (2009). "Absence of adynamic bone disease in African-Americans with CKD stage 5 after 3 years of vitamin D therapy guided by iPTH and the PTH-(1-84)/N-terminally truncated PTH fragments ratio." Clin Nephrol **71**(3): 267-75.

[Article Request Form](#)

Henry Ford Health System, Detroit, Michigan.

BACKGROUND: Secondary hyperparathyroidism is a frequent complication of chronic kidney disease (CKD). The goal of treatment is to achieve circulating levels of parathyroid hormone (PTH) associated without oversuppression of bone turnover. This is commonly achieved by treatment with vitamin D analogs. Doses of vitamin D compounds are usually monitored by measurement of circulating levels of PTH. **STUDY DESIGN:** To prospectively assess the effects on bone histology of two different protocols for dosing vitamin D. **SETTING AND PARTICIPANTS:** African-American patients from the same geographic area, managed by the same team of physicians in three dialysis clinics were studied. Patients were treated with vitamin D for 3 years and underwent bone biopsies for assessment of bone turnover. Dosing of vitamin D during the 3 years prior to the biopsy was done following two different guidelines. One group was treated following K/DOQI guidelines adapted to the bio-intact PTH assay (Protocol A), the other group was managed (Protocol B) following K/DOQI guidelines for intact PTH and/or the ratio of PTH-(1-84)/N-terminally truncated fragments (PTH ratio). **PREDICTOR:** Levels of circulating PTH and/or PTH ratio. **OUTCOME:** Prevalence of low bone turnover. **MEASUREMENTS:** Qualitative and quantitative assessment of bone histology after tetracycline labeling. **RESULTS:** 7 out of 22 patients managed following Protocol A were found to have low bone turnover (32%) by bone histology. None of the 21 patients managed by Protocol B for guidance of vitamin D therapy, had low bone turnover. **LIMITATIONS:** Lack of bone biopsy at the beginning of study. **CONCLUSIONS:** This report indicates that the additional information provided by the PTH ratio represents a distinct advantage in avoiding

low bone turnover over the use of a single PTH assay to guide vitamin D dosing in African-American patients with CKD Stage 5 on dialysis.

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Nephrology

Novak, J. E. and L. A. Szczech (2009). "Phosphate binders in chronic kidney disease and end-stage renal disease: A patient-centered approach." *Seminars in Dialysis* **22**(1): 56-63.

[PDF Full-Text](#)

Disorders of calcium and phosphorus metabolism are associated with significant morbidity and mortality in patients with advanced chronic kidney disease. These patients typically require oral phosphate binders to maintain phosphorus homeostasis, but the choice of which among several agents to use has been actively investigated and debated. Recent debate has been polarized between those who favor calcium-based binders for their proven efficacy and relatively low cost and those who favor sevelamer for its putative beneficial effects on inflammatory biomarkers and vascular calcification. This review summarizes the current state of the art of prescribing phosphate binders, ranging from large-scale clinical trials to focused mechanistic studies, and proposes that the available evidence does not conclusively prove the relative superiority of any one binder.

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Nephrology

Yee, J., G. Zasuwa, S. Frinak and A. Besarab (2009). "Hemoglobin variability and hyporesponsiveness: much ado about something or nothing?" *Adv Chronic Kidney Dis* **16**(2): 83-93.

[PDF Full-Text](#)

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Hemoglobin (Hb) variability is considered a discrete clinical entity that when present may presage poor clinical outcomes. However, Hb variability is an intrinsic property of biological systems and is present in all patients, those with and without the anemia of chronic kidney disease. Taken together, variability actually represents the integration of multiple influences at multiple levels in the life of a red cell, namely the summation of positive and negative influences on erythropoiesis. Thus, Hb variability may be interpreted as a mathematic function of time and is the result of a host of influences including definition of the normal Hb range, native erythron responsiveness/hyporesponsiveness, temporal changes in endogenous and exogenous erythropoiesis-stimulating agent (ESA) levels, the algorithms used to dose ESAs and their duration of action, the presence of biologically available iron, red cell turnover, and recyclable and non-recyclable blood loss and gain. When viewed within this construct of matrixed determinants, the source of hemoglobin variability is more readily identified. When variability is present but the etiology is not easily discerned, erythropoietic hyporesponsiveness must be considered and evaluated. Finally, integration of all of these concepts is possible within the context of an anemia management protocol.

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Neurology

Athiraman, H., Q. Jiang, G. L. Ding, L. Zhang, Z. G. Zhang, L. Wang, A. S. Arbab, Q. J. Li, S. Panda, K. Ledbetter, A. M. Rad and M. Chopp (2009). "Investigation of relationships between transverse relaxation rate, diffusion coefficient, and labeled cell concentration in ischemia rat brain using MRI." *Magnetic Resonance in Medicine* **61**(3): 587-94.

[PDF Full-Text](#)

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 x R-2 in vitro. In contrast, in vivo labeled cell; concentration did not significantly correlate with R-2, ADC, and ADC x 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

Chopp, M., Y. Li and Z. G. Zhang (2009). "Mechanisms underlying improved recovery of neurological function after stroke in the rodent after treatment with neurorestorative cell-based therapies." Stroke **40**(3 Suppl): S143-5. [PDF Full-Text](#)

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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

Chopp, M., A. Mahmood, D. Lu and Y. Li (2009). "Mesenchymal stem cell treatment of traumatic brain injury." J Neurosurg. EPub Ahead of Print. [PDF Full-Text](#)

Departments of Neurology and Neurosurgery, Henry Ford Health System, Detroit, Michigan.

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Neurology

Knight, R. A., K. Karki, J. R. Ewing, G. W. Divine, J. D. Fenstermacher, C. S. Patlak and T. N. Nagaraja (2009). "Estimating blood and brain concentrations and blood-to-brain influx by magnetic resonance imaging with step-down infusion of Gd-DTPA in focal transient cerebral ischemia and confirmation by quantitative autoradiography with Gd-[(14)C]DTPA." J Cereb Blood Flow Metab. EPub Ahead of Print. [Article Request Form](#)

Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA Department of Physics, Oakland University, Rochester, Michigan, USA.

An intravenous step-down infusion procedure that maintained a constant gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) blood concentration and magnetic resonance imaging (MRI) were used to localize and quantify the blood-brain barrier (BBB) opening in a rat model of transient cerebral ischemia (n=7). Blood-to-brain influx rate constant (K(i)) values of Gd-DTPA from such regions were estimated using MRI-Patlak plots and compared with the K(i) values of Gd-[(14)C]DTPA, determined minutes later in the same rats with an identical step-down infusion, quantitative autoradiography (QAR), and single-time equation. The normalized plasma concentration-time integrals were identical for Gd-DTPA and Gd-[(14)C]DTPA, indicating that the MRI protocol yielded reliable estimates of plasma Gd-DTPA levels. In six rats with a BBB opening, 14 spatially similar regions of extravascular Gd-DTPA enhancement and Gd-[(14)C]DTPA leakage, including one very small area, were observed. The terminal tissue-plasma ratios of Gd-[(14)C]DTPA tended to be slightly higher than those of Gd-DTPA in these regions, but the differences were not significant. The MRI-derived K(i) values for Gd-DTPA closely agreed and correlated well with those obtained for Gd-[(14)C]DTPA. In summary, MRI estimates of Gd-DTPA concentration in the plasma and brain and the influx rate are quantitatively and spatially accurate with step-down infusions.

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Neurology

LeWitt, P. A. (2009). "Levodopa for Parkinson's Disease - reply." N Engl J Med **360**(9): 936.

[PDF Full-Text](#)

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Neurology

LeWitt, P. A. (2009). "Levodopa therapeutics for Parkinson's disease: New developments." Parkinsonism Relat Disord **15**(Suppl 1): S31-S34. [Article Request Form](#)

Levodopa serves as the gold standard of anti-parkinsonian therapy and nearly every patient with Parkinson's disease eventually receives this drug. To improve upon levodopa therapy, several forms of treatment have been devised to augment its actions. and new delivery systems are under development. This new research offers promise for improving outcomes with this highly effective therapy.

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Neurology

Li, L., Q. Jiang, G. Ding, L. Zhang, Z. G. Zhang, Q. Li, S. Panda, A. Kapke, M. Lu, J. R. Ewing and M. Chopp (2009). "MRI identification of white matter reorganization enhanced by erythropoietin treatment in a rat model of focal ischemia." Stroke **40**(3): 936-41. [PDF Full-Text](#)

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BACKGROUND AND PURPOSE: The objectives of the present study were to: (1) noninvasively identify white matter reorganization and monitor its progress within 6 weeks after the onset of stroke; and (2) quantitatively investigate the effect of recombinant human erythropoietin treatment on this structural change using in vivo measurement of diffusion anisotropy. **METHODS:** Male Wistar rats were subjected to middle cerebral artery occlusion and treated with recombinant human erythropoietin intraperitoneally at a dose of 5000 U/kg of body weight (n=11) or the same volume of saline (n=7) daily for 7 days starting 24 hours after middle cerebral artery occlusion. MRI measurements of T2- and diffusion-weighted images and cerebral blood flow were performed and neurological severity score was assessed at 1 day and weekly for 6 weeks after middle cerebral artery occlusion. Luxol fast blue and Bielschowsky staining were used to demonstrate myelin and axons, respectively. **RESULTS:** White matter reorganization occurred along the ischemic lesion boundary after stroke. The region of white matter reorganization seen on the tissue slice coincided with the elevated area on the fractional anisotropy map, which can be accurately identified. The increase in elevated fractional anisotropy pixels corresponded with progress of white matter reorganization and was associated with improvement of neurological function. Treatment with recombinant human erythropoietin after stroke significantly enhanced white matter reorganization, restored local cerebral blood flow, and expedited functional recovery. **CONCLUSIONS:** White matter reorganization can be detected by fractional anisotropy. Elevated fractional anisotropy pixels may be a good MRI index to stage white matter remodeling and predict functional outcome.

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Neurology

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

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

Stroke increases neuroblasts in the subventricular zone (SVZ) of the lateral ventricle and these neuroblasts migrate toward the ischemic boundary to replace damaged neurons. Using brain slices from the nonischemic adult rat and transgenic mice that expressed enhanced green fluorescent protein (EGFP) concomitantly with doublecortin (DCX), a marker for migrating neuroblasts, we recorded electrophysiological characteristics while simultaneously analyzing the gene expression in single SVZ cells. We found that SVZ cells expressing the DCX gene from the nonischemic rat had a mean resting membrane potential (RMP) of -30 mV. DCX-EGFP-

positive cells in the nonischemic SVZ of the transgenic mouse had a mean RMP of -25 ± 7 mV and did not exhibit Na(+) currents, characteristic of immature neurons. However, DCX-EGFP-positive cells in the ischemic SVZ exhibited a hyperpolarized mean RMP of -54 ± 18 mV and displayed Na(+) currents, indicative of more mature neurons. Single-cell multiplex RT-PCR analysis revealed that DCX-EGFP-positive cells in the nonischemic SVZ of the transgenic mouse expressed high neural progenitor marker genes, Sox2 and nestin, but not mature neuronal marker genes. In contrast, DCX-EGFP-positive cells in the ischemic SVZ expressed tyrosine hydroxylase, a mature neuronal marker gene. Together, these data indicate that stroke changes gene profiles and the electrophysiology of migrating neuroblasts.

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Neurology

Shen, L. H., Y. Li, Q. Gao, S. Savant-Bhonsale and M. Chopp (2008). "Down-regulation of neurocan expression in reactive astrocytes promotes axonal regeneration and facilitates the neurorestorative effects of bone marrow stromal cells in the ischemic rat brain." *Glia* **56**(16): 1747-54. PMC2575136. [PDF Full-Text](#)

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

The glial scar, a primarily astrocytic structure bordering the infarct tissue inhibits axonal regeneration after stroke. Neurocan, an axonal extension inhibitory molecule, is up-regulated in the scar region after stroke. Bone marrow stromal cells (BMSCs) reduce the thickness of glial scar wall and facilitate axonal remodeling in the ischemic boundary zone. To further clarify the role of BMSCs in axonal regeneration and its underlying mechanism, the current study focused on the effect of BMSCs on neurocan expression in the ischemic brain. Thirty-one adult male Wistar rats were subjected to 2 h of middle cerebral artery occlusion followed by an injection of 3×10^6 rat BMSCs ($n = 16$) or phosphate-buffered saline ($n = 15$) into the tail vein 24 h later. Animals were sacrificed at 8 days after stroke. Immunostaining analysis showed that reactive astrocytes were the primary source of neurocan, and BMSC-treated animals had significantly lower neurocan and higher growth associated protein 43 expression in the penumbral region compared with control rats, which was confirmed by Western blot analysis of the brain tissue. To further investigate the effects of BMSCs on astrocyte neurocan expression, single reactive astrocytes were collected from the ischemic boundary zone using laser capture microdissection. Neurocan gene expression was significantly down-regulated in rats receiving BMSC transplantation ($n = 4$ /group). Primary cultured astrocytes showed similar alterations; BMSC coculture during reoxygenation abolished the up-regulation of neurocan gene in astrocytes undergoing oxygen-glucose deprivation ($n = 3$ /group). Our data suggest that BMSCs promote axonal regeneration by reducing neurocan expression in peri-infarct astrocytes.

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Neurology

Smith, H., G. Sinson and P. Varelas (2009). "Vasopressors and propofol infusion syndrome in severe head trauma." *Neurocrit Care* **10**(2): 166-72. [Article Request Form](#)

Propofol infusion syndrome (PRIS) is a rare, but lethal complication of high-dose propofol infusions. We undertook this study to evaluate the incidence of PRIS in a cohort of patients with severe head trauma and its relation to the use of vasopressors.

We reviewed all patients with severe head trauma admitted to our Neuro-Intensive Care Unit over a 4-year period for use of propofol and vasopressors. Those patients who developed unexplained acidosis, creatine kinase elevation unrelated to trauma, and electrocardiographic changes were considered having PRIS. We investigated the concomitant use of vasopressors while propofol was used and calculated odds ratios for developing PRIS.

We report three adult patients who developed PRIS out of 50 (6%) admitted patients with severe head trauma on propofol infusions. Two of these patients survived and one expired after withdrawal of life support. Concomitant use of vasopressors was associated with development of PRIS in this cohort (odds ratio 29, 95% CI 1.5-581, $P < 0.05$).

Awareness and early recognition of PRIS in critically ill neurosurgical patients on vasopressors and daily screening for creatine kinase elevation, unexplained acidosis, or electrocardiographic changes may reduce the incidence and case-fatality.

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Neurology

Wang, L. C., M., R. L. Zhang, L. Zhang, Y. LeTourneau, Y. F. Feng, A. Jiang, D. C. Morris and Z. G. Zhang (2009). "The Notch pathway mediates expansion of a progenitor pool and neuronal differentiation in adult neural progenitor cells after stroke." Neurosci **158**(4): 1356-63. [PDF Full-Text](#)

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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Neurology

Xu, J., X. F. Liu, J. L. Chen, A. Zacharek, X. Cui, S. Savant-Bhonsale, Z. G. Liu and M. Chopp (2009). "Simvastatin enhances bone marrow stromal cell differentiation into endothelial cells via notch signaling pathway." Am J Physiol Cell Physiol **296**(3): C535-C543. [PDF Full-Text](#)

Bone marrow stromal cells (BMSCs) are capable of differentiating into multiple cell lineages including endothelial cells. Simvastatin, an HMG-CoA reductase inhibitor that is used as a cholesterol-lowering agent, promotes endothelial differentiation from epithelial progenitor cells (EPC). The Notch signaling pathway, which plays a key role in multiple cell functions such as differentiation, proliferation, and apoptosis, can be regulated by simvastatin. Therefore, we examined the effect of simvastatin on BMSC differentiation into endothelial cells and the underlying mechanisms involved in this process. We observed that simvastatin stimulation of rat BMSCs resulted in significantly increased expression of endothelial-specific genes and proteins, including von Willebrand factor (vWF), CD31, vascular endothelial-cadherin (VE-cadherin), vascular endothelial growth factor receptor-2 (VEGFR2, Flk-1), and VEGF receptor 1 (VEGFR-1, Flt-1). Simvastatin also significantly increased capillary tubelike formation of the BMSCs. In addition, the intracellular cleavage of Notch (NICD) was markedly enhanced by simvastatin in BMSCs. Incubation of BMSCs with a gamma-secretase inhibitor, or Notch1 small interfering RNA (siRNA) that significantly inhibited the formation of NICD, blocked the expression of endothelial-specific markers in BMSCs and their differentiation into functional endothelial cells. These data suggest that simvastatin induces rat BMSCs differentiation into endothelial cells via a Notch signaling pathway.

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Neurosurgery

Kole, M., B. Amin, H. Marin, A. Russman and W. Sanders (2009). "Intracranial angioplasty and stent placement for direct cerebral revascularization of nonacute intracranial occlusions and near occlusions." Neurosurg Focus **26**(3): E3. [Article Request Form](#)

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mkole1@hfhs.org

OBJECT: The authors reviewed their experience in 7 cases of nonacute intracranial occlusions and near occlusions in which the patients underwent intracranial angioplasty and stent implantation for direct cerebral revascularization. METHODS: Between 2005 and 2008, 4 men and 3 women underwent direct cerebral revascularization of nonacute intracerebral occlusions or near occlusions. Five patients had chronic angiographically documented occlusion and 2 patients had chronic angiographically documented near occlusions. The locations of the treated vessels included 2 supraclinoid internal carotid arteries, 4 middle

cerebral arteries, and 1 vertebral artery. Prior to intervention, all patients were symptomatic and experienced strokes ipsilateral to their occlusions. In addition, all patients had clinical or radiographic evidence of ongoing hemodynamic compromise. Five patients underwent successful intracranial angioplasty and stent placement and 2 patients underwent successful intracranial balloon angioplasty alone. The mean time from documented vessel occlusion to treatment was 35 days. All patients had successful revascularization determined using the Thrombolysis in Cerebral Infarction (TICI) scale: TICI Score 3, 2b, and 2a in 4, 2, and 1 patient, respectively, and the mean residual stenosis was 38%. RESULTS: After uneventful technical procedures, 1 patient suffered a perforator vessel stroke and 1 patient suffered a fatal hemorrhage. Mean modified Rankin Scale score of 2 (range 1-5) and mean Glasgow Outcome Scale score of 4 (range 1-6) were achieved during a mean clinical follow-up period of 399 days (range 1-840 days). Asymptomatic restenosis was documented in 4 patients, 1 underwent bypass retreatment, and 1 patient received repeated balloon angioplasty. CONCLUSIONS: Combined intracranial angioplasty and stent placement is a potential treatment option in selected patients for the direct revascularization of nonacute intracranial occlusions and near occlusions. Whether this represents a substantial risk reduction compared with the best medical therapy or a long-lasting treatment option is unknown.

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Neurosurgery

Xiong, Y., A. Mahmood and M. Chopp (2009). "Emerging treatments for traumatic brain injury." Expert Opin Emerg Drugs **14**(1): 67-84. [Article Request Form](#)

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

BACKGROUND: This review summarizes promising approaches for the treatment of traumatic brain injury (TBI) that are in either preclinical or clinical trials. OBJECTIVE: The pathophysiology underlying neurological deficits after TBI is described. An overview of select therapies for TBI with neuroprotective and neurorestorative effects is presented. METHODS: A literature review of preclinical TBI studies and clinical TBI trials related to neuroprotective and neurorestorative therapeutic approaches is provided.

RESULTS/CONCLUSION: Nearly all Phase II/III clinical trials in neuroprotection have failed to show any consistent improvement in outcome for TBI patients. The next decade will witness an increasing number of clinical trials that seek to translate preclinical research discoveries to the clinic. Promising drug- or cell-based therapeutic approaches include erythropoietin and its carbamylated form, statins, bone marrow stromal cells, stem cells singularly or in combination or with biomaterials to reduce brain injury via neuroprotection and promote brain remodeling via angiogenesis, neurogenesis, and synaptogenesis with a final goal to improve functional outcome of TBI patients. In addition, enriched environment and voluntary physical exercise show promise in promoting functional outcome after TBI, and should be evaluated alone or in combination with other treatments as therapeutic approaches for TBI.

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Other

Schwarz, D. A., A. M. Jamali, M. S. Kakwan, A. Fregene, K. G. Arman and S. R. Buchman (2009). "Biomechanical assessment of regenerate integrity in irradiated mandibular distraction osteogenesis." Plast Reconstr Surg **123**(2): 114S-122S. [PDF Full-Text](#)

Background: The role of mandibular distraction osteogenesis for reconstructing mandibular defects following radiation therapy depends on the quality of attenuated bone healing in the regenerate. This study investigated the regenerate properties after radiation therapy using yield and breaking load. The authors hypothesized that both would be significantly reduced in mandibular distraction osteogenesis following radiation therapy compared with mandibular distraction osteogenesis alone.

Methods: Male Sprague-Dawley rats underwent left mandibular fractionated 36-Gy preoperative external beam radiation therapy and then 2 weeks of recovery (n = 7) or no radiation therapy (n = 10) before surgery. External fixators were secured and unilateral osteotomies were created behind the third molar, followed by 4 days of latency and then mandibular distraction osteogenesis: 0.3 mm every 12 hours for 8 days (5.1 mm) and 4 weeks of consolidation. Unoperated controls received no radiation therapy (n = 13). Mandibles were tension tested at 0.5 mm/second to failure, and yield and breaking load were determined.

Results: There was a significantly lower breaking load for mandibular distraction osteogenesis following radiation therapy compared with mandibular distraction osteogenesis, alone, but there was no significant difference in yield between the groups. Both groups had significantly lower breaking load and yield when compared with unoperated controls.

Conclusions: The lowered breaking load in mandibular distraction osteogenesis following radiation therapy reflects the reduced biomechanical quality of the regenerate, despite evidence of radiographic union. These data show that radiographic union is not an adequate outcome measure for regenerate healing and support the need to define quantitative bone-healing metrics in mandibular distraction osteogenesis following radiation therapy before implementation in head and neck reconstruction.

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Other

Shabari, E. R., R. M. Delgado, B. Kar, A. Civitello, P. Loyalka, B. Czerska, M. Klapbolz, E. Haeusslein, S. Brown and M. A. Konstam (2009). "Clinical and hemodynamic findings with a system for delivery of aortic flow therapy in patients with acute decompensated heart failure." J Heart Lung Transplant **28**(2): S84. [PDF Full-Text](#)

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Otolaryngology

Duffy, S. A., D. L. Ronis, S. McLean, K. E. Fowler, S. B. Gruber, G. T. Wolf and J. E. Terrell (2009). "Pretreatment Health Behaviors Predict Survival Among Patients With Head and Neck Squamous Cell Carcinoma." J Clin Oncol. Epub Ahead of Print. [PDF Full-Text](#)

Departments of Otolaryngology, Psychiatry, Internal Medicine, Epidemiology, and Human Genetics, University of Michigan Medical School; School of Nursing, University of Michigan; Ann Arbor Veterans Affairs (VA) Center for Clinical Management Research, VA Ann Arbor Healthcare System, Ann Arbor; and Department of Otolaryngology, Henry Ford Health System, Detroit, MI.

PURPOSE: Our prior work has shown that the health behaviors of head and neck cancer patients are interrelated and are associated with quality of life; however, other than smoking, the relationship between health behaviors and survival is unclear. **PATIENTS AND METHODS:** A prospective cohort study was conducted to determine the relationship between five pretreatment health behaviors (smoking, alcohol, diet, physical activity, and sleep) and all-cause survival among 504 head and neck cancer patients. **RESULTS:** Smoking status was the strongest predictor of survival, with both current smokers (hazard ratio [HR] = 2.4; 95% CI, 1.3 to 4.4) and former smokers (HR = 2.0; 95% CI, 1.2 to 3.5) showing significant associations with poor survival. Problem drinking was associated with survival in the univariate analysis (HR = 1.4; 95% CI, 1.0 to 2.0) but lost significance when controlling for other factors. Low fruit intake was negatively associated with survival in the univariate analysis only (HR = 1.6; 95% CI, 1.1 to 2.1), whereas vegetable intake was not significant in either univariate or multivariate analyses. Although physical activity was associated with survival in the univariate analysis (HR = 0.95; 95% CI, 0.93 to 0.97), it was not significant in the multivariate model. Sleep was not significantly associated with survival in either univariate or multivariate analysis. Control variables that were also independently associated with survival in the multivariate analysis were age, education, tumor site, cancer stage, and surgical treatment. **CONCLUSION:** Variation in selected pretreatment health behaviors (eg, smoking, fruit intake, and physical activity) in this population is associated with variation in survival.

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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. PMC2605778. [PDF Full-Text](#)

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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

Syamal, M. N. and G. M. Gardner (2009). "Operative adaptation for endoscopic identification of Zenker's diverticulum." Laryngoscope. EPub Ahead of Print. [PDF Full-Text](#)

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Pathology

Dhar, J. P., L. Gregoire, W. Lancaster, A. Stark, A. Schwartz, D. Schultz, L. Essenmacher, J. Ager, L. Chiodo, M. Husain and R. J. Sokol (2009). "cervical enoplasia and high risk humanpapillomavirus in systemic erythematosus." Reprod Sci **16**(3): 153A. [Article Request Form](#)

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Pathology

Zarbo, R. J., J. M. Tuthill, R. D'Angelo, R. Varney, B. Mahar, C. Neuman and A. Ormsby (2009). "The Henry Ford Production System: reduction of surgical pathology in-process misidentification defects by bar code-specified work process standardization." Am J Clin Pathol **131**(4): 468-77. [PDF Full-Text](#)

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

Misidentification defects are a potential patient safety issue in medicine, including in the surgical pathology laboratory. In addressing the Joint Commission's national patient safety goal of accurate patient and specimen identification, we focused our lens internally on our own laboratory processes, with measurement tools designed to identify potential misidentification defects and their root causes. Based on this knowledge, aligned with our lean work culture in the Henry Ford Production System, we redesigned our surgical pathology laboratory workflow with simplified connections and pathways reinforced by a bar code technology innovation to specify and standardize work processes. We also adopted just-in-time prestain slide labeling with solvent-impervious, bar-coded slide labels at the microtome station, eliminating the loop-back pathway of poststain, batch slide matching, and labeling with adhesive paper labels. These changes have enabled us to dramatically reduce the overall misidentification case rate by approximately 62% with an approximate 95% reduction in the more common histologic slide misidentification defects while increasing technical throughput at the histology microtomy station by 125%.

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Pharmacy

Pindolia, V. K., L. Stebelsky, T. M. Romain, L. Luoma, S. N. Nowak and F. Gillanders (2009). "Mitigation of medication mishaps via medication therapy management." *Ann Pharmacother* **43**(4): 611-20. [PDF Full-Text](#)

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BACKGROUND: In 2006, the Center for Medicare & Medicaid Services incorporated the requirement for a Medication Therapy Management Program (MTMP) for individuals with Part D coverage to ensure that drug regimens provide optimal therapeutic outcomes through improved medication use, thereby reducing adverse drug events. **OBJECTIVE:** To evaluate the effectiveness of an MTMP implemented for Medicare Advantage Prescription Drug members enrolled with Health Alliance Plan (HAP) during 2006 and 2007. **METHODS:** Patient eligibility for MTMP was searched electronically. Clinical pharmacists researched medication histories and adherence and, through telephone contact, ascertained the patients' healthcare goals and needs. A patient-centered pharmacotherapy plan was created and implemented collaboratively with the patient's physician(s). To ensure that therapy goals were met, pharmacists performed follow-up interventions. Clinical outcomes and cost savings were compared for MTMP enrollees versus those declining enrollment. **RESULTS:** Average enrollment rate for the MTMP was 20% for 2006 and 2007. Nearly 60% of interventions involved changing therapy to improve efficacy and greater than 40% involved changing therapy to improve safety. Analysis of 2006 data revealed an overall improvement in electronically measurable clinical outcomes for MTMP enrollees versus individuals who declined enrollment, including a trend toward improved adherence to drug therapy for heart failure, insulin use, and a significant reduction in gastrointestinal bleeds ($p = 0.001$). Cost-savings analysis indicated a greater reduction in total prescription per member per month costs (\$PMPM) of 17.2% for MTMP enrollees versus a 7% reduction for those who declined MTMP ($p = 0.001$). Patients who enrolled into the 2006 MTMP also saw a sustained positive effect in lowered \$PMPM for prescription drugs in 2007. **CONCLUSIONS:** The HAP MTMP, conducted through telephone contacts, produced positive trends in improving clinical outcomes, reductions in pharmacy costs, and sustained pharmacy cost savings for patients who enrolled in the MTMP compared with patients who declined enrollment.

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Pulmonary

Azzato, E. M., L. M. Morton, A. W. Bergen, S. S. Wang, N. Chatterjee, P. Kvale, M. Yeager, R. B. Hayes, S. J. Chanock and N. E. Caporaso (2009). "SLC6A3 and body mass index in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial." *BMC Med Genetics* **10**(9). [Article Request Form](#)

Background: To investigate the contribution of the dopamine transporter to dopaminergic reward-related behaviors and anthropometry, we evaluated associations between polymorphisms at the dopamine transporter gene (SLC6A3) and body mass index (BMI), among participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Methods: Four polymorphisms (rs6350, rs6413429, rs6347 and the 3' variable number of tandem repeat (3' VNTR) polymorphism) at the SLC6A3 gene were genotyped in 2,364 participants selected from the screening arm of PLCO randomly within strata of sex, age and smoking history. Height and weight at ages 20 and 50 years and baseline were assessed by questionnaire. BMI was calculated and categorized as underweight, normal, overweight and obese (< 18.5, 18.5-24.9, 25.0-29.9, or ≥ 30 kg/m²), respectively). Odds ratios (ORs) and 95% confidence intervals (CIs) of SLC6A3 genotypes and haplotypes were computed using conditional logistic regression.

Results: Compared with individuals having a normal BMI, obese individuals at the time of the baseline study questionnaire were less likely to possess the 3' VNTR variant allele with 9 copies of the repeated sequence in a dose-dependent model (** is referent; OR*9 = 0.80, OR99 = 0.47, P-trend = 0.005). Compared with individuals having a normal BMI at age 50, overweight individuals (A-C-G-* is referent; ORA-C-G-9 = 0.80, 95% CI 0.65-0.99, $p = 0.04$) and obese individuals (A-C-G-* is referent; ORA-C-G-9 = 0.70, 95% CI 0.49-0.99, $p = 0.04$) were less likely to possess the haplotype with the 3' variant allele (A-C-G-9).

Conclusion: Our results support a role of genetic variation at the dopamine transporter gene, SLC6A3, as a modifier of BMI.

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Radiation Oncology

Elshaikh, M. A., W. Underwood and D. E. Soto (2009). "Androgen deprivation therapy for patients with prostate carcinoma and Parkinson's disease: Case report and review of the literature." *Can J Urol* **16**(1): 4495-7. [Article Request Form](#)

We report a case history of a patient with Parkinsons disease (PD) treated with androgen deprivation therapy (ADT) and external beam radiation for prostate cancer, who developed severe deterioration of his PD during ADT.

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Radiation Oncology

Jin, J. Y., M. Ajlouni, F. M. Kong, S. Ryu, I. J. Chetty and B. Movsas (2008). "Utilize target motion to cover clinical target volume (ctv)--a novel and practical treatment planning approach to manage respiratory motion." *Radiother Oncol* **89**(3): 292-303. [Article Request Form](#)

Department of Radiation Oncology, Henry Ford Hospital, Detroit, MI 48202, USA.
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PURPOSE: To use probability density function (PDF) to model motion effects and incorporate this information into treatment planning for lung cancers. MATERIAL AND METHODS: PDFs were calculated from the respiratory motion traces of 10 patients. Motion effects were evaluated by convolving static dose distributions with various PDFs. Based on a differential dose prescription with relatively lower dose to the clinical target volume (CTV) than to the gross tumor volume (GTV), two approaches were proposed to incorporate PDFs into treatment planning. The first approach uses the GTV-based internal target volume (ITV) as the planning target volume (PTV) to ensure full dose to the GTV, and utilizes the motion-induced dose gradient to cover the CTV. The second approach employs an inhomogeneous static dose distribution within a minimized PTV to best match the prescription dose gradient. RESULTS: Motion effects on dose distributions were minimal in the anterior-posterior (AP) and lateral directions: a 10-mm motion only induced about 3% of dose reduction in the peripheral target region. The motion effect was remarkable in the cranial-caudal direction. It varied with the motion amplitude, but tended to be similar for various respiratory patterns. For the first approach, a 10-15 mm motion would adequately cover the CTV (presumed to be 60-70% of the GTV dose) without employing the CTV in planning. For motions < 10-mm, an additional PTV with a margin inversely related to the motion was needed to cover the CTV. The second approach was used for motions > 15-mm. An example of inhomogeneous static dose distribution in a reduced PTV was given, and it showed significant dose reduction in the normal tissue without compromising target coverage. CONCLUSIONS: Respiratory motion-induced dose gradient can be utilized to cover the CTV and minimize the lung dose without the need for more sophisticated technologies.

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Radiation Oncology

Kodali, G., S. U. Siddiqui and R. J. Stanley (2009). "Charge Redistribution in Oxidized and Semiquinone E. coli DNA Photolyase upon Photoexcitation: Stark Spectroscopy Reveals a Rationale for the Position of Trp382." *J Am Chem Soc* **131**(13): 4795-807. [Article Request Form](#)

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122, and
Department of Radiation Oncology, Henry Ford Hospital, Detroit, Michigan 48202.

The electronic structure of the two lowest excited electronic states of FAD and FADH(*) in folate-depleted E. coli DNA photolyase (PL(OX) and PL(SQ), respectively) was measured using absorption Stark spectroscopy. The experimental analysis was supported by TDDFT calculations of both the charge redistribution and the difference dipole moments for the transitions of both oxidation states using lumiflavin as a model. The difference dipole moments and polarizabilities for PL(OX) are similar to those obtained in our previous work for flavins in simple solvents and in an FMN-containing flavoprotein. No such comparison can be made for PL(SQ), as we believe this to be the first experimental report of the direction and magnitude of excited-state charge redistribution in any flavosemiquinone. The picture that emerges from these studies is discussed in the context of electron transfer in photolyase, particularly for the semiquinone photoreduction process, which

involves nearby tryptophan residues as electron donors. The direction of charge displacement derived from an analysis of the Stark spectra rationalizes the positioning of the critical Trp382 residue relative to the flavin for efficient vectorial electron transfer leading to photoreduction. The ramifications of vectorial charge redistribution are discussed in the context of the wider class of flavoprotein blue light photoreceptors.

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Radiation Oncology

Patel, M., F. Siddiqui, J. Y. Jin, T. Mikkelsen, M. Rosenblum, B. Movsas and S. Ryu (2009). "Salvage reirradiation for recurrent glioblastoma with radiosurgery: Radiographic response and improved survival." J Neurooncol **92**(2): 185-91. [PDF Full-Text](#)

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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Sleep Medicine

Khalid, I., L. Rana, T. J. Khalid and T. Roehrs (2009). "Refractory restless legs syndrome likely caused by olanzapine." J Clin Sleep Med **5**(1): 68-9. PMC2637170. [PDF Full-Text](#)

Henry Ford Health System, 2799 W Grand Blvd, CFP-3, Detroit, MI 48202, USA.

We report a case of severe restless legs syndrome (RLS) that occurred as a side effect of olanzapine therapy. It was refractory to treatment with 2 mg of clonazepam and 3 mg ropinirole. There was partial relief with propoxyphene, however, it was stopped because of side effects. The symptoms disappeared once olanzapine was switched to another antipsychotic medication. Only two prior published reports associate olanzapine usage with development of RLS. In one report, low-dose benzodiazepines and ropinirole were associated with resolution of RLS symptoms stating dopamine depletion as the likely etiology. In our patient, however, RLS due to olanzapine was refractory to the trial of both high-dose benzodiazepine and ropinirole. This suggests that RLS occurring as a side effect of olanzapine therapy may have additional causative mechanisms beyond simple dopamine depletion as postulated before. High-dose narcotics, if tolerated, may be an alternative in such refractory cases.

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Sleep Medicine

Richardson, G. S., G. Zammit, S. Wang-Weigand and J. Zhang (2009). "Safety and subjective sleep effects of ramelteon administration in adults and older adults with chronic primary insomnia: a 1-year, open-label study." J Clin Psychiatry. Epub Ahead of Print. [Article Request Form](#)

Henry Ford Hospital, Sleep Disorders Center, 2799 West Grand Blvd., CFP-3, Detroit, MI 48202. gsl@attglobal.net.

OBJECTIVE: To evaluate the long-term safety and subjective sleep effects of ramelteon in adults with chronic insomnia. **METHOD:** Subjects with primary insomnia (DSM-IV-TR criteria) for ≥ 3 months received ramelteon nightly for 1 year; a 3-day placebo run out followed. Subjects aged ≥ 65 years received open-label ramelteon 8 mg (N = 248); those aged 18 to 64 years received ramelteon 16 mg (N = 965). Subjects completed sleep diaries and returned to the clinic at week 1 and at months 1, 2, 3, 4, 6, 8, 10, and 12 for safety assessments and investigator-performed Clinical Global Impressions. The study was conducted from February 2003 through September 2004. **RESULTS:** There were no noteworthy changes in vital signs, physical examinations, clinical chemistry, hematology, or urinalysis values and no electrocardiogram changes to suggest adverse cardiac effects. Endocrine values remained within normal range throughout treatment. Consistent statistically significant ($p \leq .05$) decreases in free thyroxine (in adults) and free testosterone (in older men) were detected. Duration of menses increased by approximately 1 day. A total of 40.8% of subjects reported at least 1 adverse event possibly associated with ramelteon use. The adverse events reported varied considerably, the incidence of individual adverse events was low, and the frequencies of adverse events were similar at months 6 and 12. In both groups, subjective sleep latency and total sleep time improved by month 1 and was sustained during the 1-year period. At 6 months and 1 year, Clinical Global Impressions indices were improved. During placebo run out, subjective sleep latency did increase but did not return to baseline. **CONCLUSION:** Year-long administration of ramelteon was well tolerated. Ramelteon was associated with sustained improvements in subjective sleep latency, subjective total sleep time, and Clinical Global Impressions. **TRIAL REGISTRATION:** clinicaltrials.gov Identifier: NCT00671086.

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Sleep Medicine

Roth, T. (2009). "Comorbid insomnia: current directions and future challenges." Am J Manag Care **15 Suppl**: S6-13. [PDF Full-Text](#)

Henry Ford Hospital Sleep Disorders and Research Center, 2799 W Grand Blvd, Detroit, MI 48202, USA. TRoth1@hfhs.org

Insomnia is a leading cause of absenteeism, presenteeism (lost productivity when employees are at work), accidents, and errors in the workplace. Overall direct and indirect costs exceed \$30 billion annually. A significant portion of these costs are attributable to patients with comorbid insomnia, making these conditions a significant clinical public health issue. These comorbid conditions include mood and anxiety disorders; chronic pain; respiratory, urinary, and neurologic conditions; diabetes; and cardiovascular diseases. Traditional treatment for insomnia with comorbid conditions has focused on treating the comorbid condition with the expectation that the insomnia will resolve. Recent studies, however, suggest this approach is not the most appropriate. Instead, treating both conditions simultaneously may improve the outcomes for each.

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Sleep Medicine

Schwartz, J. R. L. and T. Roth (2008). "Neurophysiology of sleep and wakefulness: Basic science and clinical implications." Curr Neuropharmacol **6(4)**: 367-78. [Article Request Form](#)

Increased attention to the prevalence of excessive sleepiness has led to a clear need to treat this symptom, thus reinforcing the need for a greater understanding of the neurobiology of sleep and wakefulness. Although the physiological mechanisms of sleep and wakefulness are highly interrelated, recent research reveals that there are distinct differences in the active brain processing and the specific neurochemical systems involved in the two states. In this review, we will examine the specific neuronal pathways, transmitters, and receptors composing the ascending arousal system that flow from the brainstem through the thalamus, hypothalamus, and basal forebrain to the cerebral cortex. We will also discuss the mutually inhibitory interaction between the core neuronal components of this arousal system and the sleep-active neurons in the ventrolateral preoptic nucleus, which serves as a brainstem-switch, regulating the stability of the sleep-wake states. In addition, we will review the role of homeostatic and circadian processes in the sleep-wake cycle, including the influence of the suprachiasmatic nucleus on coordination of sleep-wake systems. Finally, we will summarize how the above processes are reflected in disorders of sleep and wakefulness, including insomnia, narcolepsy, disorders associated with fragmented sleep, circadian rhythm sleep disorders, and primary neurological disorders such as Parkinson's and Alzheimer's diseases.

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Sleep Medicine

Zammit, G., H. Schwartz, T. Roth, S. Wang-Weigand, S. Sainati and J. Zhang (2009). "The effects of ramelteon in the first-night model of transient insomnia." [Sleep Medicine](#) **10**(1): 55-9. [PDF Full-Text](#)

Objective: To evaluate the efficacy and safety of ramelteon, a highly selective MT1/MT2 melatonin receptor agonist, for the treatment of transient insomnia in adults.

Methods: In a randomized, double-blind, placebo-controlled, multi-center Study, 289 adults naive to it sleep laboratory environment were randomized to receive it single nighttime dose of ramelteon 8 mg, 16 mg, or placebo. The primary variable was latency to persistent sleep measured by polysomnography. Additional objective and subjective sleep parameters its well as next-morning residual effects were assessed.

Results: Ramelteon 8 mg treatment significantly reduced latency to persistent sleep compared with placebo (12.2 min vs. 19.7 min, $P = 0.004$). Total sleep time was significantly increased with both ramelteon 8 mg (436.8 min, $P = 0.009$) and ramelteon 16 mg (433.1 min, $P = 0.043$) compared with placebo (419.7 min). Ramelteon did not alter sleep architecture, and no significant next-morning residual effects were detected. The incidence of adverse events was similar for the ramelteon and placebo groups and most were considered mild or moderate.

Conclusion: Ramelteon 8 mg significantly decreased latency to persistent sleep and increased total sleep time, with no significant next-morning psychomotor, memory, or cognitive effects in this first-night model of transient insomnia.

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Sleep Medicine

Roth, T. (2009). "Hypnotic use for insomnia management in chronic obstructive pulmonary disease." [Sleep Medicine](#) **10**(1): 19-25. [PDF Full-Text](#)

Chronic obstructive Pulmonary disease (COPD) is one of the leading causes of mortality and morbidity worldwide. Because of the chronic nature of the disease, optimal care for patients includes successful treatment of comorbidities that accompany COPD, including insomnia. Insomnia symptoms and associated disruption or sleep are prevalent in COPD patients but treatment with traditional benzodiazepines may compromise respiratory function. This review Summarizes the efficacy and safety consideration Of Current drugs available for the treatment of insomnia in COPI) patients including benzodiazepines, non-benzodiazepine receptor agonists such as eszopiclone, zolpidem, and zaleplon, sedating antidepressants such as trazodone, and the melatonin receptor agonist ramelteon.

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Surgery

Andrzejewski, T., D. Deeb, X. Gao, A. Danyluk, A. S. Arbab, S. A. Dulchavsky and S. C. Gautam (2008). "Therapeutic efficacy of curcumin/TRAIL combination regimen for hormone-refractory prostate cancer." [Oncol Res](#) **17**(6): 257-67. [Article Request Form](#)

Department of Surgery, Henry Ford Health System, Detroit, MI, USA.

Because of lack of effective treatment options for hormone-refractory prostate cancer at the present time, the need for developing novel therapeutic strategies and targets to treat and prevent the progression of hormone-sensitive prostate cancer to the hormone-refractory stage is paramount. Our previous in vitro studies have shown that curcumin sensitizes both hormone-sensitive and hormone-resistant prostate cancer cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and that combined curcumin/TRAIL treatment induces apoptosis in cancer cells by inhibiting antiapoptotic p-Akt and nuclear factor-kappaB (NF-kappaB). In the present study, we demonstrate that curcumin and TRAIL combination regimen is also the most effective treatment for inhibiting the growth of PC3 xenografts compared to curcumin or TRAIL monotherapy. The inhibition of PC3 tumors by combined treatment correlated with significant reduction in expression of p-Akt and NF-kappaB in tumor tissue. Furthermore, tumor growth inhibition by curcumin/TRAIL combination regimen was associated with significant decrease in cell proliferation and an increase in terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells in the tumors without significant change in

microvessel density. Based on the significant efficacy in this preclinical model, combined curcumin/TRAIL regimen may be an effective adjuvant therapy for hormone-refractory prostate cancer.

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Surgery

Frege, A., D. Ditmars and A. Siddiqui (2009). "Botulinum toxin type A: a treatment option for digital ischemia in patients with Raynaud's phenomenon." J Hand Surg [Am] **34**(3): 446-52. [Article Request Form](#)

Division of Plastic Surgery, Henry Ford Hospital, Detroit, MI, USA.

PURPOSE: Raynaud's phenomenon is an exaggerated vasospastic response that causes pallor and cyanosis. In the hand, it results in pain, disability, and the need for amputation. Current accepted medical and surgical treatments are not uniformly successful and have their inherent morbidities. Reports in the literature describe the use of botulinum toxin type A (BTX-A) for the treatment of vasospastic ischemia of the digits. We report the results of the treatment of recalcitrant digital ischemia with BTX-A in our institution. **METHODS:** We performed a retrospective chart review between January 2003 and February 2007. All patients presented with a diagnosis of Raynaud's phenomenon with worsening pain, discoloration, or nonhealing wound of the hand. Patients received BTX-A injections into the perineurovascular tissue of the wrist or the distal palm, or along the digit. Outcomes measured included pain rating, digit color and appearance, transcutaneous oxygen saturation, and healing of chronic ulcers. **RESULTS:** Twenty-six patients were treated, with a total of 55 treatment encounters. Patients were observed for an average of 18 months. Statistically significant improvements were noted for pain score and digit transcutaneous oxygen saturation measurements after treatment ($p < .05$). We found smokers and women were more likely to have improved coloration and appearance after injections. Complications included localized injection-related pain and transient intrinsic muscle weakness. **CONCLUSIONS:** Botulinum toxin type A significantly improves pain and improves healing in Raynaud's patients with few complications. BTX-A was found to be a safe and useful treatment option for vasospastic digital ischemia.

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Surgery

Velanovich, V. (2009). "Endoscopic endoluminal radiofrequency ablation of Barrett's esophagus: initial results and lessons learned." Surg Endosc. EPub Ahead of Print. [Article Request Form](#)

Division of General Surgery, K-8, Henry Ford Hospital, 2799 West Grand Blvd., Detroit, MI, 48202-2689, USA, vvelano1@hfhs.org.

BACKGROUND: Ablating Barrett's epithelium may reduce the risk of developing esophageal adenocarcinoma. This study reports the experience of a single surgeon using an endoscopic endoluminal device that delivers radiofrequency energy (the BARRx device) to ablate Barrett's esophagus. **METHODS:** All patients who underwent ablation of Barrett's epithelium with the BARRx system were reviewed for length of Barrett's metaplasia, presence of high-grade dysplasia, postprocedure complications, completeness of ablation at first follow-up endoscopy, need for additional ablation, completeness of ablation at second follow-up endoscopy, and concomitant performance of a Nissen fundoplication. **RESULTS:** Sixty-six patients underwent Barrett's ablation. The median length of the Barrett's esophagus was 3 (range, 1-14) cm. Twelve patients (18%) had high-grade dysplasia. There were no immediate procedure-related complications. Four strictures occurred: three in patients with ≥ 12 -cm segments of Barrett's and one in a 6-cm segment. Twenty-nine of 49 patients (59%) who had planned 3-month follow-up endoscopy had complete ablation. Five patients had planned two-stage ablation. Twenty patients with incomplete ablation had additional ablation. Twenty-seven patients had planned follow-up endoscopy at ≥ 1 year: 25 of 27 (93%) had biopsy-proven normal esophageal mucosa. The median length of Barrett's esophagus in patients with initially incomplete ablation was 6 cm, compared with 2 cm in the initially complete ablation patients. Seven Nissen funduplications were present at the time of ablation, whereas six were performed concomitantly with the ablation without increased difficulty. **CONCLUSIONS:** Complete ablation of Barrett's esophagus with radiofrequency endoluminal ablation is achievable in $>90\%$ of patients. Patients with longer segments are likely to require additional ablation. Patients with very long segments are at risk for stricture and should be approached cautiously. Performance of a fundoplication is not hindered by concomitant ablation.

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Urology

Boris, R. S., A. Bhandari, L. S. Krane, D. Eun, S. Kaul and J. O. Peabody (2009). "Salvage robotic-assisted radical prostatectomy: Initial results and early report of outcomes." BJU International **103**(7): 952-6. [PDF Full-Text](#)

To evaluate the initial results of salvage robotic-assisted radical prostatectomy (SRARP) after recurrence following primary radiotherapy (RT) for localized prostate cancer.

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.

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. 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 (2009). "Cell cycle-dependent effects of 3,3'-diindolylmethane on proliferation and apoptosis of prostate cancer cells." J Cell Physiol **219**(1): 94-9. [Article Request Form](#)

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

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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