

Henry Ford Health System Publication List

March 2008

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CARDIOLOGY

Kugelmass, A. D., S. Sadanandan, et al. (2006). "Early Invasive Strategy Improves Outcomes in Patients With Acute Coronary Syndrome With Previous Coronary Artery Bypass Graft Surgery: A Report From TACTICS-TIMI 18." *Crit Pathw Cardiol* **5**(3): 167-172. [PDF Full-Text](#)

From the Henry Ford Hospital, Detroit, Michigan; Oklahoma University Health Sciences Center, Oklahoma City, Oklahoma; Baylor College of Medicine Medical Center, Houston, Texas; Merck Research Laboratories, Blue Bell, Pennsylvania; University of Pennsylvania, Philadelphia, Pennsylvania; Brigham and Women's Hospital, Boston, Massachusetts; and Emory University, Atlanta, Georgia.

BACKGROUND:: Patients with previous coronary artery bypass graft surgery (CABG) have been classified as a high-risk subset of patients who experience non-ST elevation acute coronary syndrome (ACS). Recent studies suggest that an early invasive strategy is beneficial in moderate- and high-risk patients with non-ST elevation ACS. We hypothesized that an early invasive strategy is associated with improved outcomes in patients with non-ST elevation ACS with prior CABG. **METHODS AND RESULTS::** In the Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18 trial (TACTICS-TIMI 18), 2220 patients with non-ST segment elevation ACS were randomized to an early invasive or conservative (selectively invasive) strategy. All patients were treated with aspirin, heparin, and tirofiban. Four hundred eighty-four (22%) of these patients had undergone CABG before enrollment. We analyzed whether patients with previous CABG had different 6-month outcomes and whether an early invasive strategy was associated with an improvement in long-term outcomes. Prior CABG was associated with a higher risk of adverse outcomes by 6 months, including a higher rate of readmission for ACS (17.4% vs 11.0%, $P < 0.001$) and a higher incidence of the composite end point of death, myocardial infarction, or rehospitalization for ACS (22.3% vs 16.4%, $P = 0.002$). There was a trend toward a higher incidence of myocardial infarction (7.1% vs 5.3%, $P = 0.051$). An early invasive strategy was associated with a reduction in the composite of death or myocardial infarction (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.31-1.0; $P = 0.089$) and a significant reduction in the incidence of myocardial infarction at 6 months (OR, 0.44; 95% CI, 0.21-0.93; $P = 0.032$). **CONCLUSIONS::** Patients with non-ST segment elevation ACS who have had previous CABG are a high-risk subset. An early invasive strategy reduces risk of myocardial infarction in this high-risk group.

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CARDIOLOGY

McCord, J. and E. A. Amsterdam (2004). "Electron Beam Computed Tomography for Assessment of Patients Presenting to the Emergency Department With Chest Pain." *Crit Pathw Cardiol* **3**(4): 221-224. [PDF Full-Text](#)

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Hours
8:30am-9:00pm M-Th
8:30am-5:00pm F
9:00am-1:00pm Sa

From the Division of Cardiology, Henry Ford Hospital and Medical Center, Detroit, MI; and Division of Cardiovascular Medicine, University of California (Davis) Medical Center, Sacramento, CA.

Electron beam computed tomography (EBCT) is a unique, noninvasive radiologic method capable of high-resolution imaging that is being increasingly used for evaluation of the cardiovascular system. Among its multiple applications, coronary artery calcium (CAC) imaging has attracted considerable attention because of the potential of this technique for early detection of coronary artery disease (CAD), the leading cause of mortality in our society. Although measurement of CAC has been primarily performed in the outpatient setting in both symptomatic and asymptomatic subjects, several studies have assessed the utility of the method to identify CAD in patients presenting to the emergency department with chest pain suggestive of myocardial ischemia but without objective evidence of the latter. This group comprises a majority of those presenting to the emergency department with chest pain, and their safe, accurate and cost-effective evaluation has been a continuing challenge.

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CARDIOLOGY

McCord, J. K. (2004). "The future of cardiac markers in the emergency department." Crit Pathw Cardiol **3**(3): 107-9. [PDF Full-Text](#)

From Henry Ford Hospital, Heart & Vascular Institute, Detroit, Michigan.

The development of new cardiac marker strategies has the potential of improving the treatment and triage of patients in the emergency department with possible acute coronary syndrome. Although there has been a proliferation of new cardiac markers, at present rigorous studies demonstrating the incremental utility of many of these are lacking.

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CENTER FOR HEALTH PROMOTION & DISEASE PREVENTION

Davis, R. M. (2008). "British American Tobacco ghost-wrote reports on tobacco Advertising bans by the International Advertising Association and J J Boddewyn." Tob Control. **Full Text Not Available/Click for Article Request Form**

Henry Ford Health System, United States.

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

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DERMATOLOGY

Tierney, E. P. and D. J. Goldberg (2008). "Laser hair removal pearls." J Cosmet Laser Ther **10**(1): 17-23. **Full Text Not Available/Click for Article Request Form**

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

A number of lasers and light devices are now available for the treatment of unwanted hair. The goal of laser hair removal is to damage stem cells in the bulge of the follicle through the targeting of melanin, the endogenous chromophore for laser

and light devices utilized to remove hair. The competing chromophores in the skin and hair, oxyhemoglobin and water, have a decreased absorption between 690 nm and 1000 nm, thus making this an ideal range for laser and light sources. Pearls of laser hair removal are presented in this review, focusing on four areas of recent development: 1 treatment of blond, white and gray hair; 2 paradoxical hypertrichosis; 3 laser hair removal in children; and 4 comparison of lasers and IPL. Laser and light-based technologies to remove hair represents one of the most exciting areas where discoveries by dermatologists have led to novel treatment approaches. It is likely that in the next decade, continued advancements in this field will bring us closer to the development of a more permanent and painless form of hair removal.

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DIAGNOSTIC RADIOLOGY

Arbab, A. S. and J. A. Frank (2008). "Cellular MRI and its role in stem cell therapy." *Regen Med* **3**(2): 199-215.
Full Text Not Available/[Click for Article Request Form](#)

Henry Ford Hospital, Cellular & Molecular Imaging Laboratory, Department of Radiology, 1 Ford Place, 2F
Detroit, MI 48202, USA. saali@rad.hfh.edu

Hematopoietic, stromal and organ-specific stem cells are under evaluation for therapeutic efficacy in cell-based therapies of cardiac, neurological and other disorders. It is critically important to track the location of directly transplanted or infused cells that can serve as gene carrier/delivery vehicles for the treatment of disease processes and be able to noninvasively monitor the temporal and spatial homing of these cells to target tissues. Moreover, it is also necessary to determine their engraftment efficiency and functional capability following transplantation. There are various in vivo imaging modalities used to track the movement and incorporation of administered cells. Tagging stem cells with different contrast agents can make these cells probes for different imaging modalities. Recent reports have shown that stem cells labeled with iron oxides can be used as cellular MRI probes demonstrating the cell trafficking to target tissues. In this review, we will discuss the status and future prospect of stem cell tracking by cellular MRI for cell-based therapy.

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DIAGNOSTIC RADIOLOGY

Williams, T. R. and M. F. Oakes (2008). "Metastatic breast carcinoma to renal angiomyolipomas in tuberous sclerosis." *Urology* **71**(2): 352 e5-7. [PDF Full-Text](#)

Department of Radiology, Henry Ford Hospital, Detroit, Michigan 48202, USA. ikewms1@aol.com

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease manifesting as hamartomatous involvement of several organs, including brain, kidneys, skin, heart, lungs, and retina. We report the first case of a patient with TSC, with large bilateral renal angiomyolipomas (AML), who developed multiple soft tissue masses within her primarily fatty AMLs, resulting from metastatic breast cancer.

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ENDOCRINOLOGY & METABOLISM

Kruger, D. F. (2007). "New landscape of type 2 diabetes management." *J Am Acad Nurse Pract* **19**(11 Suppl 1): 5-10. [PDF Full-Text](#)

Division of Endocrinology, Diabetes, and Bone Disorders, Henry Ford Medical Center, Detroit, Michigan, USA.

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ENDOCRINOLOGY & METABOLISM

Vollbrecht, J. E. and D. S. Rao (2008). "Images in clinical medicine. Tumor-induced osteomalacia." *N Engl J Med* **358**(12): 1282. [PDF Full-Text](#)

Henry Ford Health System, Detroit, MI 48202, USA. tjvollbrecht@yahoo.com

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HYPERTENSION & VASCULAR RESEARCH

Yee, J. (2008). "Chronic kidney disease--a disease domain complex." *Geriatrics* **63**(3): 30-7. **Full Text Not Available/Click for Article Request Form**

Wayne State University and Henry Ford Hospital, Detroit, MI.

Chronic kidney disease (CKD) is a silent disorder that is under-recognized. It is most often diagnosed by biochemical abnormalities. The combination of age, ethnicity, gender, and serum creatinine yields the best overall index of kidney function, and the estimated glomerular filtration rate (GFR) must be readily available for clinical practitioners to facilitate identification of CKD. The detection of persistent proteinuria also heralds the presence of CKD, but this sign is often ignored. A detailed case study is presented to demonstrate the evolution of CKD and its insidious progression to a multifaceted and complex disorder. Delineation of the complications of CKD permits the adaptation of a collaborative action plan between primary care physicians and nephrologists, and sample approaches are outlined.

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INTERNAL MEDICINE

Sinno, M. C., M. Kowalski, et al. (2008). "R-wave amplitude changes measured by electrocardiography during early transmural ischemia." *J Electrocardiol*. **Full Text Not Available/Click for Article Request Form**

Henry Ford Hospital, Detroit, MI.

BACKGROUND: Changes in the amplitude of the R wave (RWA) on the electrocardiogram (ECG) have been described during acute myocardial ischemia and infarction. However, this has not been well studied in a controlled setting. We hypothesized that significant increase in RWA occurs during early transmural myocardial ischemia. **METHODS:** We prospectively evaluated changes in RWA in 50 patients during brief episodes of transmural ischemia induced by first balloon occlusion (mean, 38 seconds at 6-10 atmospheric pressures) during elective percutaneous coronary intervention. We recorded 12-lead ECGs at 20-second intervals before and during balloon inflation in 16 right coronary arteries, 14 left circumflex arteries, and 20 left anterior descending arteries. R wave amplitude was digitally measured in each of the 12 leads in every ECG using the ECG interval editor (General Electric HC, Menomonee Falls, WI). Intracoronary (IC) ECGs were also recorded in 4 patients. The mean of the RWA in each lead before balloon inflation was compared to the mean RWA during balloon inflation. **RESULTS:** R wave amplitude significantly increased during balloon inflation from baseline in limb leads I, II, aVL, and all the precordial leads with the exception of lead V(1). The RWA increase did not reach statistical significance in leads III, aVF, and V(1). Mean RWA increase was consistent in all leads except aVR during the brief episodes of ischemia during initial balloon inflation because of the inverse polarity of this lead. The increase in RWA was seen in most patients (mean, 75%) in whom transmural ischemia was induced by first balloon inflation. Besides, the RWA showed an increase from baseline in 3 patients who had IC-lead recordings. **CONCLUSION:** R wave amplitude increases significantly in precordial leads (V(2)-V(6)) and limb leads (I, II, aVL) of the surface ECG during brief episodes of transmural ischemia. The increase in RWA might be consistent with the expansion of the left ventricular cavity during ischemia and/or alterations in conduction that are intrinsic to the myocardium.

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INTERNAL MEDICINE

Williams, L. K., J. Oliver, et al. (2008). "Gene-environment interactions between CD14 C-260T and endotoxin exposure on Foxp3+ and Foxp3- CD4+ lymphocyte numbers and total serum IgE levels in early childhood." *Ann Allergy Asthma Immunol* **100**(2): 128-36. **PDF Full-Text**

Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan 48202, USA. kwillia5@hfhs.org

BACKGROUND: Innate immune system stimuli, such as endotoxin, seem to affect allergy risk. Previously, we described gene-environment interactions between the endotoxin receptor polymorphism C-260T of the CD14 gene and endotoxin exposure on total serum IgE level; however, the mechanism of this interaction is not known. **OBJECTIVE:** To examine whether this gene-environment interaction affects early CD4(+)Foxp3(-) or CD4(+)Foxp3(+) lymphocyte numbers. **METHODS:**

Participating children were part of a birth cohort in the Detroit metropolitan area. Participants were genotyped for the CD14 C-260T polymorphism. Endotoxin exposure was estimated from dust measured in the home when children were 6 months old. Intracellular Foxp3 protein expression, a regulatory T-cell marker, was used to characterize CD4(+) lymphocytes in blood samples collected at the age of 12 months; total serum IgE level was also measured at this time. Because race/ethnicity may confound or modify genetic associations, all analyses were stratified by race/ethnicity. RESULTS: We observed a significant gene-environment interaction between CD14 C-260T genotype and endotoxin exposure on CD4(+) lymphocyte numbers, particularly CD4(+)Foxp3(-) lymphocytes. Stratified analyses suggest effect modification by race/ ethnicity on CD4(+) Foxp3(+) lymphocyte numbers, with a significant interaction in African American children but not in white children. The interaction between CD14 C-260T genotype and endotoxin exposure on total IgE levels was opposite that observed for CD4(+) lymphocyte numbers, suggesting reciprocal relationships. CONCLUSIONS: A gene-environment interaction between endotoxin and CD14 C-260T genotype on IgE levels may be the result of an upstream, opposing effect on CD4(+)Foxp3(+) and CD4(+)Foxp3(-) lymphocyte numbers. Race/ethnicity may affect which of these cell populations is affected by this gene-environment interaction.

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NEUROLOGY

Ding, G., Q. Jiang, et al. (2008). "Angiogenesis Detected After Embolic Stroke in Rat Brain Using Magnetic Resonance T2*WI." *Stroke*. **Full Text Not Available/Click for Article Request Form**

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

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

BACKGROUND AND PURPOSE: This study uses T2* weighted imaging (T2*WI) to measure the temporal evolution of cerebral angiogenesis in rats subjected to embolic stroke up to 6 weeks after stroke onset with or without sildenafil treatment. Method-Male Wistar rats were subjected to embolic stroke and treated with saline (n=10) or with sildenafil (n=11), with treatment initiated at 24 hours and continued daily for 7 days after onset of ischemia. T2*WI measurements were performed at 24 hours after embolization and weekly up to 6 weeks using a 7-Tesla system. Histological measurements were obtained at 6 weeks after MRI scans. RESULTS: Using T2*WI, cerebral angiogenesis was detected starting from 4 weeks and from 2 weeks after onset of embolic stroke in saline and sildenafil treated rats, respectively. Significant differences in the temporal and spatial features of angiogenesis after embolic stroke up to 6 weeks after onset of stroke were found between saline and sildenafil treated rats and were identified with T2*WI. MRI permeability parameter, Ki, complementarily detected angiogenesis after ischemia in embolic stroke rats. Sildenafil treatment of stroke rats significantly enhanced the angiogenesis, as confirmed histologically. CONCLUSIONS: T2*WI can quantitatively measure the temporal evolution of angiogenesis in rats subjected to embolic stroke. Compared to control rats, sildenafil treatment significantly increased angiogenesis in treated animals up to 6 weeks after stroke.

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NEUROLOGY

Gao, Q., Y. Li, et al. (2008). "Bone marrow stromal cells reduce ischemia-induced astrocytic activation in vitro." *Neuroscience* **152**(3): 646-55. [PDF Full-Text](#)

Department of Neurology, Henry Ford Health System, Education and Research Building, #3056, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

Transplantation of bone marrow stromal cells (BMSCs) improves animal neurological functional recovery after stroke. To obtain insight into the mechanisms underlying the therapeutic benefit, we directed our attention to the interaction of BMSCs with astrocytes. Astrocytes become reactive (astrogliosis) after a brain injury, such as stroke. Astrogliosis plays both beneficial and detrimental roles in brain recovery. Previously, we have shown that administration of BMSCs to animals with stroke significantly reduces the thickness of the scar wall formed by reactive astrocytes. We tested the influence of mouse bone marrow stromal cell (mBMSC) on astrogliosis under oxygen-glucose deprivation (OGD)/reoxygenation conditions in vitro, employing an anaerobic chamber. Our data indicate that mBMSCs down-regulate glial fibrillary acidic protein

(GFAP) expression in astrocytes after 2 h of OGD and an additional 16 h reoxygenation. mBMSCs protected astrocytes from ischemia, maintaining morphological integrity and proliferation. The IL-6/IL-6R/gp130 pathway is associated with astrogliosis in response to CNS disorders. Therefore, we examined the effects of mBMSC on the IL-6/IL-6R/gp130 pathway as an underlying mechanism of mBMSC-altered astrogliosis. Furthermore, IL-6 siRNA was used to block IL-6 expression in astrocytes to further investigate IL-6 involvement in mBMSC-altered astrogliosis. Our results indicate that the mBMSC-conferred decline of astrogliosis post-ischemia may derive from the down-regulation of the IL-6/IL-6R/gp130 pathway.

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NEUROLOGY

Zheng, X., F. Jiang, et al. (2008). "Sensitization of cerebral tissue in nude mice with photodynamic therapy induces ADAM17/TACE and promotes glioma cell invasion." *Cancer Lett.* **Full Text Not Available/Click for Article Request Form**

Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202, USA.

In the present study, we tested the hypothesis that a mild cerebral tissue injury promotes subsequent glioma invasion via activation of the ADAM17-EGFR-PI3K-Akt pathway. Mild injury was induced by photodynamic therapy (PDT), which employs tissue-penetrating laser light exposure following systemic administration of a tumor-localizing photosensitizer. Athymic nude mice were treated with sublethal PDT (80J/cm² with 2mg/kg Photofrin). Hypoxic stress and ADAM17-EGFR-PI3K-Akt were measured using Western blot and immunostaining. Additional groups with/without pro-sublethal PDT were subsequently implanted with U87 glioma tumor cell. Tumor invasion and ADAM17-EGFR-PI3K-Akt pathway in tumor area were measured. After a sublethal dose of PDT, HIF-1 α expression was increased by a factor of three in PDT-treated normal brain tissue compared to contralateral control brain tissue. PDT-treated brain tissue exhibited a significant increase in ADAM17, p-EGFR, p-Akt expression compared to non-treated tissue. ADAM17 positive area significantly increased from 1.78% to 10.89%. The percentage of p-EGFR and p-Akt positive cells significantly increased from 9.50% and 14.50% to 21.31% and 32.29%, respectively, PDT treatment significantly increased subsequent implanted U87 glioma cell invasion by 3.68-fold and increased ADAM17, EGFR, p-EGFR, Akt, p-Akt expression by 178%, 43.9%, 152.7%, 89.6%, and 164.2%, respectively, compared to control group. Our data showed that a sublethal sensitization of cerebral tissue with PDT significantly increased U87 cell invasion in nude mice, and that glioma cell invasion is highly correlated with activation of the ADAM17-EGFR-PI3K-Akt pathway ($r=0.928, 0.775, 0.870, 0.872, \text{ and } 0.883$, respectively), most likely via HIF-1 α .

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NEUROSURGERY

Jiang, W., S. Cazacu, et al. (2008). "FK506 binding protein mediates glioma cell growth and sensitivity to rapamycin treatment by regulating NF-kappaB signaling pathway." *Neoplasia* **10**(3): 235-43. [PDF Full-Text](#)

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

FK506 binding protein 5 (FKBP5) belongs to a family of immunophilins named for their ability to bind immunosuppressive drugs, also known as peptidyl-prolyl cis-trans isomerases, and also with chaperones to help protein folding. Using glioma cDNA microarray analysis, we found that FKBP5 was overexpressed in glioma tumors. This finding was further validated by real-time reverse transcription-polymerase chain reaction and Western blot analysis. The roles of FKBP5 in glioma cells were then examined. We found that cell growth was suppressed after FKBP5 expression was inhibited by short interfering RNA transfection and enhanced by FKBP5 overexpression. Electrophoretic mobility shift assay showed that nuclear factor-kappa B (NF-kappaB) and DNA binding was enhanced by FKBP5 overexpression. The expression level of I-kappa B alpha and phosphorylated NF-kappaB was regulated by the expression of FKBP5. These data suggest that FKBP5 is involved in NF-kappaB pathway activation in glioma cells. In addition, FKBP5 overexpression in rapamycin-sensitive U87 cells blocked the cells' response to rapamycin treatment, whereas rapamycin-resistant glioma cells, both PTEN-positive and -negative, were synergistically sensitive to rapamycin after FKBP5 was knocked down, suggesting that the FKBP5 regulates glioma cell response to rapamycin treatment. In conclusion, our study demonstrates that FKBP5 plays an important role in glioma growth and chemoresistance through regulating signal transduction of the NF-kappaB pathway.

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NEUROSURGERY

Lehman, N. L. (2008). "Central nervous system tumors with ependymal features: a broadened spectrum of primarily ependymal differentiation?" *J Neuropathol Exp Neurol* **67**(3): 177-88. [PDF Full-Text](#)

Hermelin Brain Tumor Center, Henry Ford Health System, Detroit, MI 48202, USA. nllehman@yahoo.com

Ependymomas are well-characterized central nervous system (CNS) tumors that occur most often in children and young adults. Several other CNS tumor entities, including astroblastoma, chordoid glioma, papillary tumor of the pineal region, angiocentric glioma, and pilomyxoid astrocytoma, variably display histopathologic features of ependymal differentiation. The ependymal differentiation in some of these tumors is generally accepted, whereas in others, it is controversial. This article briefly reviews ependymal cell development and conventional ependymomas, the pathologic findings and clinical behavior of tumors with variable ependymal features, and the rationales for their inclusion with ependymomas or exclusion from a larger family of ependymal tumors. These issues are addressed in the context of early morphologic insights of Bailey and Cushing, Friede, and others; contemporary oncologic concepts; and recent relevant molecular and tumor stem cell studies.

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NEUROSURGERY

Yunker, C. K., W. Golembieski, et al. (2008). "SPARC-induced increase in glioma matrix and decrease in vascularity are associated with reduced VEGF expression and secretion." *Int J Cancer*. Epub Ahead of Print. [PDF Full-Text](#)

Barbara Jane Levy Laboratory of Molecular Neuro-Oncology, Hermelin Brain Tumor Center, Department of Neurosurgery, Henry Ford Hospital, Detroit, MI.

Glioblastomas are heterogeneous tumors displaying regions of necrosis, proliferation, angiogenesis, apoptosis and invasion. SPARC, a matricellular protein that negatively regulates angiogenesis and cell proliferation, but enhances cell deadhesion from matrix, is upregulated in gliomas (Grades II-IV). We previously demonstrated that SPARC promotes invasion while concomitantly decreasing tumor growth, in part by decreasing proliferation of the tumor cells. In other cancer types, SPARC has been shown to influence tumor growth by altering matrix production, and by decreasing angiogenesis via interfering with the VEGF-VEGFR1 signaling pathway. We therefore examined whether the SPARC-induced decrease in glioma tumor growth was also, in part, due to alterations in matrix and/or decreased vascularity, and assessed SPARC-VEGF interactions. The data demonstrate that SPARC upregulates glioma matrix, collagen I is a constituent of the matrix and SPARC promotes collagen fibrillogenesis. Furthermore, SPARC suppressed glioma vascularity, and this was accompanied by decreased VEGF expression and secretion, which was, in part, due to reduced VEGF165 transcript abundance. These data indicate that SPARC modulates glioma growth by altering the tumor microenvironment and by suppressing tumor vascularity through suppression of VEGF expression and secretion. These experiments implicate a novel mechanism, whereby SPARC regulates VEGF function by limiting the available growth factor. Because SPARC is considered to be a therapeutic target for gliomas, a further understanding of its complex signaling mechanisms is important, as targeting SPARC to decrease invasion could undesirably lead to the growth of more vascular and proliferative tumors. (c) 2008 Wiley-Liss, Inc.

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OTHER

Johnson, C. C., R. T. Burkman, et al. (2008). "Longitudinal study of depot medroxyprogesterone acetate (Depo-Provera(R)) effects on bone health in adolescents: study design, population characteristics and baseline bone mineral density." *Contraception* **77**(4): 239-48. **Full Text Not Available/Click for Article Request Form**

Henry Ford Hospital, Detroit, MI 48202-3450, USA.

BACKGROUND: This analysis was conducted to assess the baseline data and design methodology within an observational longitudinal comparison of use vs. nonuse of the injectable (intramuscular) contraceptive depot medroxyprogesterone acetate (DMPA-IM) and its effect on bone mass in adolescent women. STUDY DESIGN: A prospective, observational, open-

label, unmatched-cohort, safety study in females aged 11-18 years. Participants either self-selected DMPA-IM (Depo-Provera(R)) 150 mg to be administered every 12 weeks for up to 240 weeks with a 120-week post-treatment follow-up or were nonusers (users of nonhormonal contraception or sexually abstinent) who were to be followed up for up to 360 weeks. As each participant entered the study, bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry at the lumbar spine, hip and femoral neck regions, along with total body bone mineral content; serum and urine specimens were obtained for assay of bone metabolism markers and participants' histories of parity and tobacco and alcohol use were obtained. RESULTS: A total of 389 participants were enrolled: 169 elected to begin DMPA-IM; 26 chose nonhormonal methods and 194 were abstinent. The baseline characteristics indicated significant disparities between DMPA-IM users and nonusers: compared with the nonusers, DMPA-IM users had more advanced chronologic and gynecologic ages, were more likely to have smoked, been pregnant and included more blacks. These factors would likely influence bone accretion rates independent of DMPA-IM exposure. Comparison of participant BMDs with standard reference data revealed that the study cohorts did not match reference populations closely enough to make a direct between-cohort comparative analysis feasible. CONCLUSIONS: The baseline differences in cohort characteristics preclude a meaningful comparison of mean BMD changes over time between DMPA-IM users and nonusers cohorts, and comparisons of changes in Z-scores between cohorts were also not appropriate. Therefore, within-participant BMD decreases from baseline were established as safety thresholds, and the proportion of individuals crossing those thresholds on a persistent or progressive basis was identified as the revised primary end point.

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OTHER

Loper, J. E., M. D. Henkels, et al. (2008). "Isolation and Identification of Rhizoxin Analogs from *Pseudomonas fluorescens* Pf-5 using a Genomic Mining Strategy." *Appl Environ Microbiol*. **Full Text Not Available/Click for Article Request Form**

United States Department of Agriculture, Agricultural Research Service, Horticultural Crops Research Laboratory, Corvallis, OR 97330, USA; Henry Ford Health System, Detroit, MI 48202, USA; Institute for Pharmaceutical Biology, University of Bonn, 53115 Bonn, Germany.

The products synthesized from a hybrid polyketide synthase/nonribosomal peptide synthetase gene cluster in the genome of *Pseudomonas fluorescens* Pf-5 were identified using a genomics-guided strategy involving insertional mutagenesis and subsequent metabolite profiling. Five analogs of rhizoxin, a 16-membered macrolide with antifungal, phytotoxic, and antitumor activities, were produced by Pf-5 but not by a mutant with an insertion in the gene cluster. The five rhizoxin analogs, one of which has not been described previously, were differentially toxic to two agriculturally-important plant pathogens, *Botrytis cinerea* and *Phytophthora ramorum*. The rhizoxin analogs also caused swelling of rice roots, a symptom characteristic of rhizoxin itself, but were less toxic to pea and cucumber roots. Of the rhizoxin analogs produced by Pf-5, the predominant compound WF-1360 F and the newly-described compound 22Z-WF-1360 F were most toxic against the two plant pathogens and three plant species. These rhizoxin analogs were tested against a panel of human cancer lines, and they exhibited potent but non-selective cytotoxicity. This study highlights the value of the genomic sequence of the soil bacterium *P. fluorescens* Pf-5 in providing leads for the discovery of novel metabolites with significant biological properties.

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PATHOLOGY

Saglam, O., M. Salama, et al. (2008). "Immunohistochemical staining of palisading basal cells in Bowen's disease and basal involvement in actinic keratosis: contrasting staining patterns suggest different cells of origin." *Am J Dermatopathol* **30**(2): 123-6. [PDF Full-Text](#)

Department of Pathology, Henry Ford Hospital, Detroit, MI 48202, USA. osaglam@hotmail.com

Actinic keratosis (AK) and Bowen's disease (BD) are common patterns of in situ squamous cell carcinoma of the epidermis. In AK, atypical keratinocytes proliferate in the lower portion of the epidermis including the basal layer. In contrast, BD features atypical squamous cells in all portions of the epidermis but initially leaves basal cells in palisades along the basement membrane. To characterize immunohistochemically keratinocyte proliferation in AK and Palisading Basal Cells (PBC) in BD, we stained microarray samples of 45 AK and 25 BD with Molecular Immunology Borstel (MIB-1). Subsequent immunostaining of full mounted sections examined 11 BD, 7 AK, and 4 examples of psoriasis for MIB-1 (as a proliferative marker) and p53 (as

a cell cycle regulatory marker). AK stained for MIB-1 and p53 antibodies only in lower portion of epidermis and included the basal layer. BD with typical PBCs stained positive for both markers throughout the epidermis, except for the basal layer. Psoriatic biopsies stained positively for the 2 markers only in the basal and parabasal layers. Normal epidermis adjacent to the lesions in AK and BD biopsies stained sparsely in the basal layers. The correlation of different histologic patterns of epidermal involvement with different immunohistochemical patterns of stains argues for different cells of origin for BD versus AK. Lack of expression of proliferative antigens in palisading basal cells in BD provides evidence that PBCs are not the cell of origin for BD. Conversely in AK, expression of MIB-1 and p53 in basal cells argues that these cells play a role in histogenesis of AK.

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SURGERY

Carlin, A. M., K. M. Yager, et al. (2008). "Vitamin D depletion impairs hypertension resolution after Roux-en-Y gastric bypass." *Am J Surg* **195**(3): 349-52; discussion 352. [PDF Full-Text](#)

Department of Surgery, Henry Ford Hospital Detroit, MI, USA. acarlin1@hfhs.org

BACKGROUND: Morbid obesity is a risk factor for hypertension (HTN) and vitamin D (VitD) depletion. Gastric bypass (GBP) resolves HTN in many patients. The goal of this study was to evaluate the potential role of VitD nutritional status on HTN resolution in patients undergoing GBP. **METHODS:** A retrospective review of morbidly obese patients taking antihypertensive medications and undergoing GBP from September 1, 2002, through February 28, 2006 was performed. **RESULTS:** At 1 year postoperatively HTN resolved in 53%, improved in 36%, and was unchanged in 11%. Sex, race, body mass index, and percentage of excess weight loss did not impact HTN resolution. Younger patients experienced a greater rate of HTN resolution. Patients with VitD depletion had significantly lower rates of HTN resolution compared to those with adequate levels of VitD (42% vs 61%; P = .008). **CONCLUSIONS:** VitD nutritional status impacts the resolution rate of HTN after GBP. All morbidly obese patients undergoing GBP should be monitored and treated for VitD depletion.

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UROLOGY

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Purpose: The successful completion of robot-assisted renal surgery requires optimal port placement in order to minimize arm collisions due to the bulky nature of the robotic system. We describe a novel technique of port placement to maximize range of motion during robotic renal surgery that has been used successfully in over 50 procedures and report on our results. **Methods:** Five primary ports are placed utilizing a 30 degrees lens facing upward. The camera is in the most laterally placed port between the anterior axillary line and the midclavicular line, 3 to 4 cm below the costal margin. Two 8-mm robotic ports are placed 10 to 11 cm away from the camera port, triangulated towards the kidney. Assistant ports, if desired, are located medially and placed supra- (12 mm) and infraumbilically (5 mm). **Results:** This technique resulted in the camera arm residing in an upward position, moving in a completely separate plane from the working robotic arms. We had no incidents of arm-camera collision in this position. We have used this port placement technique successfully in over 50 cases performed entirely robotically. We have had no need to change port location, redock the robotic system, or add additional ports during a procedure. **Conclusion:** We report on a port placement technique for robotic renal surgery that optimizes motion of the robotic arms, while eliminating external collisions. Placement of the camera port laterally and robotic ports anteromedially results in considerable flexibility of robotic arm movement.

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