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Anh, D., B. Dudar, et al. (2006). "Acquired isolated left pulmonary vein stenosis: a complication of bronchogenic cyst removal diagnosed by transesophageal echocardiography." *Echocardiography* **23**(1): 73-4. **Full-Text Not Available** / [Click for Article Request Form](#)

Beierwaltes, W. H. (2006). "cGMP stimulates renin secretion in vivo by inhibiting phosphodiesterase-3." *Am J Physiol Renal Physiol*. [PDF Full-Text](#)

The interaction between renin, nitric oxide (NO) and its second messenger cGMP is controversial. cAMP is the stimulatory second messenger for renin, but is degraded by phosphodiesterases (PDEs). We have previously reported that increasing endogenous cGMP in rats by inhibiting its breakdown by PDE-5 stimulated renin secretion rate (RSR). This could be reversed by selective inhibition of neuronal nitric oxide synthase (nNOS). PDE-3 metabolizes cAMP, but this can be inhibited by cGMP, suggesting that renal cGMP could stimulate RSR by diminishing PDE-3 degradation of cAMP. Rats were anesthetized with Inactin prior to determination of blood pressure (BP), renal blood flow (RBF) and sampling of renal venous and arterial blood to determine RSR. In 13 rats, basal BP was 104 +/- 2 mm Hg, RBF was 6.1 ml/min/gkw and RSR was 2.9 +/- 1.4 ng AngI/hr/min. Inhibiting PDE-5 with 20 mg/kg bw ip Zaprinast did not change hemodynamic parameters, but increased RSR 5-fold to 12.2 +/- 4.9 ng AngI/hr/min (p<0.05). Renal venous cAMP was increased by Zaprinast from 93.8 +/- 27.9 to 149.2 +/- 36.0 pM/min/gkw (p<0.05). When another 10 rats were treated with the PDE-3 inhibitor Milrinone (0.4 microg/min over 30 min, which did not affect hemodynamics), RSR was elevated to 10.4 +/- 4.4 ng AngI/hr/min. Milrinone also increased renal venous cAMP from 212 +/- 29 to 304 +/- 29 pM/min/gkw (p<0.025). Administration of Zaprinast to rats pretreated with Milrinone (n=10) did not further increase in RSR (7.5 +/- 3.3 ng AngI/hr/min). These results are consistent with endogenous renal cGMP inhibiting PDE-3, which diminishes renal metabolism of cAMP. The resulting increase in cAMP serves as an endogenous stimulus for renin secretion. This suggests a pathway by which NO can indirectly stimulate RSR through its second messenger cGMP.

Benninger, M. S., S. C. Payne, et al. (2006). "Endoscopically directed middle meatal cultures versus maxillary sinus taps in acute bacterial maxillary rhinosinusitis: a meta-analysis." *Otolaryngol Head Neck Surg* **134**(1): 3-9. [PDF Full-Text](#)

OBJECTIVE: The aim of this study was to verify the correlation of endoscopically directed middle meatal (EDMM) cultures with maxillary sinus tap and culture (MST) in acute bacterial rhinosinusitis (ABRS). **STUDY DESIGN AND METHODS:** Meta-analysis of the previous literature, unpublished data, and a prospective trial supported by the Sinus & Allergy Health Partnership. EDMM and MST cultures were obtained and their results compared. Inclusion for both the unpublished and prospective trial as well as prior published literature in the meta-analysis required the studies to compare EDMM versus MST in the acute setting of bacterial rhinosinusitis with both symptomatic and radiologic evidence of ABRS. **RESULTS:** Three articles and 1 national presentation were identified for inclusion. Additional data from unpublished studies and the prospective trial were combined. The pooled data consisted of 126 patients with 131 culture pairs. For known pathogenic bacteria for ABRS and in comparison to MST, EDMM had a sensitivity of 80.9%, a specificity of 90.5%, a positive predictive value of 82.6%,

a negative predictive value of 89.4%, and an overall accuracy of 87.0% (95% confidence interval, 81.3%-92.8%); 70.5% (12/17) of false positive culture pairs were of known pathogens for ABRS that would not be expected to be contaminants. **CONCLUSIONS AND SIGNIFICANCE:** This meta-analysis shows that EDMM is a highly sensitive and accurate culture method for acute ABRS and may be more sensitive than MST given the presence of pathogenic bacteria not found on antral lavage. EDMM is a viable, and possibly preferred, culture method for determining antimicrobial efficacy and bacterial resistance patterns. EBM rating: A-1a.

Besarab, A. (2006). "Access monitoring is worthwhile and valuable." *Blood Purif* **24**(1): 77-89. [PDF Full-Text](#)

During the past several years, a limited number of small clinical trials have questioned the role of surveillance in the management of vascular accesses, since the prolongation of access longevity until replacement was not altered. Although prolongation of access life span is an important endpoint, it is not the only one. Reduction in thrombotic events reduces the risks to the patient resulting from loss of access patency. The body of evidence suggests that the detection of stenosis and prevention of thrombosis are valuable. When a test indicates the likely presence of a stenosis, venography or fistulography should be used to definitely establish the presence and the degree of the stenosis. In most cases, angioplasty should be performed if the stenosis is greater than 50% by diameter. The value of routine use of any surveillance technique for detecting anatomic stenosis alone without concomitant functional assessment by measurement of access flow, venous pressure, recirculation, or other physiologic parameter has not been established. Stenotic lesions should not be repaired merely because they are present. If such correction is performed, then intra-procedural studies of access flow or intra-access pressure prior to and following percutaneous transluminal angioplasty should be conducted to demonstrate a functional improvement with a 'successful' percutaneous transluminal angioplasty.

Billecke, C., I. Malik, et al. (2006). "Analysis of glioma cell platinum response by metacomparison of two-dimensional chromatographic proteome profiles." *Mol Cell Proteomics* **5**(1): 35-42. **Full-Text Not Available / [Click for Article Request Form](#)**

Successful clinical development of cancer treatments is aided by the development of molecular markers that allow the identification of patients likely to respond. In the case of broadly cytotoxic drugs, such as the multinuclear series of platinum chemotherapeutic agents that we are evaluating for the treatment of glioma, one route to marker identification is proteomic profiling. We are using the two-dimensional chromatography system, the ProteomeLab PF2D, to compare proteomic profiles of glioma cells in culture before and after drug treatment. The existing software tools allowed the rapid identification of peaks increased by treatment of a given drug as compared with control untreated cells. To compare across these pairs, we developed new software, called the MetaComparison Tool (MCT). The MCT uses the chromatographic characteristics of peaks as identifiers, an approach that was validated by mass spectrometry of two independent isolations of a peak, from cells that were treated with two different platinum compounds. The MCT made it possible to rapidly query whether a given peak responded to more than one treatment and so allowed the identification of peaks that were specific to a given drug. As a result, this analysis greatly reduced the list of peaks whose isolation and downstream analysis by mass spectrometry is warranted, accelerating the search for protein markers of response.

Deeb, D., X. Gao, et al. (2006). "Vaccination with leukemia-loaded dendritic cells eradicates residual disease and prevent relapse." *J Exp Ther Oncol* **5**(3): 183-93. **Full-Text Not Available / [Click for Article Request Form](#)**

We have previously demonstrated that TNF-alpha gene therapy with myeloid progenitor cells inhibits the progression of 32Dp210 myeloid leukemia in mice. Because TNF-alpha has been shown to induce the activation and maturation of dendritic cells (DCs), we investigated the efficacy of DC-based leukemia vaccine for eradication of residual disease when administered following cytoreductive therapy. Immunization with DC cells loaded with 32Dp210 myeloid leukemia cells (32Dp210 vaccine) was far more effective in preventing the development of leukemia compared to immunization with irradiated leukemia cells alone. The resistance to leukemia could be adoptively transferred to naive mice with the spleen cells of mice immunized with DC-32Dp210 vaccine, and splenic cells responsible for adoptive transfer of resistance were identified as CD90 + T lymphocytes. Development of immunity in vaccinated mice was associated with the generation of leukemia specific cytotoxic T lymphocytes (CTLs) and secretion of cytokines TNF-alpha and IFN-gamma. Further, immunization with DC-32Dp210 vaccine following cytoreductive therapy with Cytosan was effective in eradicating residual disease in approximately 50

percent of the animals. However, eradication of residual disease was significantly improved (approximately 74%) when animals were treated with DC-32Dp210 vaccine in which DCs were activated with TNF-alpha prior to loading of 32Dp210 leukemia cells. Cured mice were in molecular remission since Bcr/Abl oncogene could not be amplified from the DNA isolated from the marrow, spleen, or liver of cured mice. Taken together, these data demonstrate the efficacy of DC-based leukemia vaccine for eradication of residual disease and prevention of relapse.

Eide, M. J. and M. A. Weinstock (2006). "Public health challenges in sun protection." *Dermatol Clin* **24**(1): 119-24. **Full-Text Not Available / [Click for Article Request Form](#)**

Sunscreens are a popular choice for protection from ultraviolet radiation, and hence, important components in the public health campaign to reduce the burden of skin cancer. Public health messages in skin cancer prevention have been used effectively in educational campaigns. The benefits of sunscreen extend beyond skin cancer prevention into other aspects of health and disease prevention: sunscreen decreases the risk for sunburn during physical activity outdoors and seems not to increase the risk for osteoporosis. Public health efforts have laid a solid foundation on which to face the continuing challenge of promoting and developing effective public health campaigns and health policies that encourage sunscreen use, sun protection, and the primary prevention of skin cancer. In this article, the controversies, concerns, and challenges of sunscreen use as it relates to public health are discussed.

Herrera, M., G. Silva, et al. (2006). "A high-salt diet dissociates NO synthase-3 expression and NO production by the thick ascending limb." *Hypertension* **47**(1): 95-101. **[PDF Full-Text](#)**

NO produced by endothelial NO synthase (NOS3) decreases sodium transport by the thick ascending limb (THAL). We found previously that 7 days of high salt (HS) increased THAL-NOS3 expression but not NO production. NOS3 phosphorylation regulates enzyme activity. We hypothesized that HS acutely increases NOS3 expression and NO production, and, over time, changes in NOS3 phosphorylation dissociate NO production from expression. NOS3 expression increased by 71+/-13%, 127+/-24%, and 69+/-16% at days 1, 3, and 7 of HS, respectively. At days 14 and 28, expression was back to normal salt. After 1 day of HS, NO production in response to 250 micromol/L L-arginine was elevated by 146% and, by day 3, returned to normal salt. Similar increases were found in response to endothelin-1. Inhibitors of NOS1/2 did not blunt the salt-induced increase in NO. Phosphorylation at Thr495, an inhibitory site, decreased by 39+/-8% at day 1 of HS and then increased by 116+/-18% at day 3. Phosphorylation at Ser633 and Ser1177 (stimulatory sites) decreased by 25% at day 1 and remained depressed at day 3. Superoxide production increased by 71% at day 1, decreased by 57% at day 3, and decreased by 55% at day 7. The NOS inhibitor L-NG-nitroarginine methyl ester did not alter superoxide levels at any time point. The addition of reduced nicotinamide-adenine dinucleotide phosphate and tetrahydrobiopterin had no effect on NO release after 3 days of HS. We conclude the following: (1) HS transiently increases NO production and NOS3 expression; (2) NOS3 expression and NO production are dissociated by HS; and (3) changes in phosphorylation explain how THAL NOS3 activity and expression are dissociated by HS.

Jin, J. Y., M. Ajlouni, et al. (2006). "A technique of using gated-CT images to determine internal target volume (ITV) for fractionated stereotactic lung radiotherapy." *Radiother Oncol* **78**(2): 177-84. **[PDF Full-Text](#)**

BACKGROUND AND PURPOSE: To develop and evaluate a technique and procedure of using gated-CT images in combination with PET image to determine the internal target volume (ITV), which could reduce the planning target volume (PTV) with adequate target coverage. **PATIENTS AND METHODS:** A skin marker-based gating system connected to a regular single slice CT scanner was used for this study. A motion phantom with adjustable motion amplitude was used to evaluate the CT gating system. Specifically, objects of various sizes/shapes, considered as virtual tumors, were placed on the phantom to evaluate the number of phases of gated images required to determine the ITV while taking into account tumor size, shape and motion. A procedure of using gated-CT and PET images to define ITV for patients was developed and was tested in patients enrolled in an IRB approved protocol. **RESULTS:** The CT gating system was capable of removing motion artifacts for target motion as large as 3-cm when it was gated at optimal phases. A phantom study showed that two gated-CT scans at the end of expiration and the end of inspiration would be sufficient to determine the ITV for tumor motion less than 1-cm, and another mid-phase scan would be required for tumors with 2-cm motion, especially for small tumors. For patients, the ITV encompassing visible tumors in all sets of gated-CT and regular spiral CT images seemed to be consistent with the target volume determined from PET images. PTV expanded from the ITV with a setup uncertainty margin

had less volume than PTVs from spiral CT images with a 10-mm generalized margin or an individualized margin determined at fluoroscopy. CONCLUSIONS: A technique of determining the ITV using gated-CT images was developed and was clinically implemented successfully for fractionated stereotactic lung radiotherapy.

Juncos, R., N. J. Hong, et al. (2006). "Differential effects of superoxide on luminal and basolateral Na⁺/H⁺ exchange in the thick ascending limb." *Am J Physiol Regul Integr Comp Physiol* **290**(1): R79-83. [PDF Full-Text](#)

Superoxide (O₂⁻) increases Na⁺ reabsorption in the thick ascending limb (THAL) by enhancing Na/K/2Cl cotransport. However, the effects of O₂⁻ on other THAL transporters, such as Na⁽⁺⁾/H⁺ exchangers, are unknown. We hypothesized that O₂⁻ stimulates Na⁽⁺⁾/H⁺ exchange in the THAL. We assessed total Na⁽⁺⁾/H⁺ exchange activity by measuring recovery of intracellular pH (pH(i)) after acid loading in isolated perfused THALs before and after adding xanthine oxidase (XO) and hypoxanthine (HX). We found that XO and HX decreased total pH(i) recovery rate from 0.26 +/- 0.05 to 0.21 +/- 0.04 pH units/min (P < 0.05), and this net inhibition decreased steady-state pH(i) from 7.52 to 7.37. Because THALs have different Na⁽⁺⁾/H⁺ exchanger isoforms on the luminal and basolateral membrane, we tested the effects of xanthine oxidase and hypoxanthine on luminal and basolateral Na⁽⁺⁾/H⁺ exchange by adding dimethylamiloride to either the bath or lumen. Xanthine oxidase and hypoxanthine increased luminal Na⁽⁺⁾/H⁺ exchange from 3.5 +/- 0.8 to 6.7 +/- 1.4 pmol.min⁽⁻¹⁾.mm⁽⁻¹⁾ (P < 0.01) but decreased basolateral Na⁽⁺⁾/H⁺ exchange from 10.8 +/- 1.8 to 6.8 +/- 1.1 pmol.min⁽⁻¹⁾.mm⁽⁻¹⁾ (P < 0.007). To ascertain whether these effects were caused by O₂⁻ or H₂O₂, we examined the ability of tempol, a superoxide dismutase mimetic, to block these effects. In the presence of tempol, xanthine oxidase and hypoxanthine had no effect on luminal or basolateral Na⁽⁺⁾/H⁺ exchange. We conclude that O₂⁻ inhibits basolateral and stimulates luminal Na⁽⁺⁾/H⁺ exchangers, perhaps because different isoforms are expressed on each membrane. Inhibition of basolateral Na⁽⁺⁾/H⁺ exchange may enhance stimulation of luminal Na⁽⁺⁾/H⁺ exchange by providing additional protons to be extruded across the luminal membrane. Together, the effects of O₂⁻ on Na⁽⁺⁾/H⁺ exchange may increase net HCO₃⁻ reabsorption by the THAL.

Ketterer, M. W., L. Wulsin, et al. (2006). "'Major' Depressive Disorder, coronary heart disease, and the DSM-IV threshold problem." *Psychosomatics* **47**(1): 50-5. [PDF Full-Text](#)

Seventy-seven patients with documented coronary heart disease (CHD) were evaluated for demographic/risk factor characteristics, Major Depressive Disorder (MDD) according to the Patient's Health Questionnaire (PHQ - Diagnostic and Statistical Manual IV criteria), and emotional distress by the Symptom Checklist 90-Revised (SCL-90-R). Early age at initial diagnosis for coronary heart disease (AAID) was used as a proxy for disease malignancy because early AAID is a known predictor of early mortality. MDD was unrelated to early AAID despite being strongly associated with all the scales of the SCL-90-R. Several of the SCL-90-R scales were significantly associated with early AAID in the sample as a whole (Depression, Interpersonal Sensitivity, Anxiety, Paranoia, and Psychoticism) and after removal of the patients meeting criteria for MDD (residual N = 54). Our results suggest a new criterion for determining whether depression, or any mental disorder, is "major": onset or aggravation of serious medical illness.

Kvale, P. A. (2006). "Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines." *Chest* **129**(1 Suppl): 147S-153S. [PDF Full-Text](#)

GOALS/OBJECTIVES: To review the scientific evidence on cough associated with tumors in the lungs. METHODS: MEDLINE literature review (through March 2004) for all studies published in the English language, including case series and case reports, since 1966 using the medical subject heading terms "cough" and "lung neoplasms." RESULTS: Primary bronchogenic carcinoma is the most common lethal neoplasm in the United States. Malignancies that arise in other organs will often metastasize to the lungs. Any form of cancer involving the lungs may be associated with cough. However, cough is far more likely to indicate involvement of the airways than the lung parenchyma because of the location of cough receptors. Cough is present in >65% of patients at the time lung cancer is diagnosed, and productive cough is present in >25% of patients. While cough as a presenting symptom of lung cancer is common, many studies have shown that lung cancer is the cause of chronic cough in <or=2% of all patients who present with a chronic cough. CONCLUSIONS: Bronchoscopy is usually indicated when there is suspicion of airway involvement by a malignancy. Conversely, bronchoscopy usually should not be performed to assess a cough for the possibility of lung cancer when there is little risk for lung cancer (nonsmokers) and when there are normal findings on a plain chest radiograph. If the lung cancer can be removed surgically, cough will

usually abate. Radiation therapy, chemotherapy (especially with gemcitabine), and endobronchial treatment methods likely will improve cough caused by lung cancer. Centrally acting narcotic antitussive agents are usually administered for the control of cough caused by lung cancer when other treatment methods fail.

Li, X. C., O. A. Carretero, et al. (2006). "Glucagon receptor-mediated extracellular signal-regulated kinase 1/2 phosphorylation in rat mesangial cells: role of protein kinase A and phospholipase C." *Hypertension* **47**(3): 580-5. [PDF Full-Text](#)

Glucagon, a major insulin counterregulatory hormone, binds to specific Gs protein-coupled receptors to activate glycogenolytic and gluconeogenic pathways, causing blood glucose levels to increase. Inappropriate increases in serum glucagon play a critical role in the development of insulin resistance and target organ damage in type 2 diabetes. We tested the hypotheses that: (1) glucagon induces proliferation of rat glomerular mesangial cells through glucagon receptor-activated phosphorylation of mitogen-activated protein kinase extracellular signal-regulated kinase 1/2 (p-ERK 1/2); and (2) this phosphorylation involves activation of cAMP-dependent protein kinase A (PKA) and phospholipase C (PLC)/[Ca²⁺]_i signaling pathways. In rat mesangial cells, glucagon (1 nM) stimulated [³H]-thymidine incorporation by 96% (P<0.01). This proliferative effect was blocked by the specific glucagon receptor antagonist [Des-His1-Glu9] glucagon (1 micromol/L; P<0.01), a mitogen-activated protein kinase/ERK kinase inhibitor PD98059 (10 micromol/L; P<0.01), a PLC inhibitor U73122 (1 micromol/L; P<0.01), or a PKA inhibitor H-89 (1 micromol/L; P<0.01). The proliferation was associated with a 2-fold increase in p-ERK 1/2 that peaked 5 minutes after glucagon stimulation (P<0.01) and also was blocked by [Des-His1-Glu9] glucagon. Total ERK 1/2 was not affected by glucagon. Pretreating of mesangial cells with U73122 or H89 significantly attenuated ERK 1/2 phosphorylation induced by glucagon. We believe that these are the first data showing that glucagon activates specific receptors to induce ERK 1/2 phosphorylation and thereby increase mesangial cell proliferation and that this effect of glucagon involves both PLC/[Ca²⁺]_i- and cAMP-dependent PKA-activated signaling cascades.

Li, Y., K. McIntosh, et al. (2006). "Allogeneic bone marrow stromal cells promote glial-axonal remodeling without immunologic sensitization after stroke in rats." *Exp Neurol.* **Full-Text Not Available** / [Click for Article Request Form](#)

We evaluated the effects of allogeneic bone marrow stromal cell treatment of stroke on functional outcome, glial-axonal architecture, and immune reaction. Female Wistar rats were subjected to 2 h of middle cerebral artery occlusion. Rats were injected intravenously with PBS, male allogeneic ACI - or syngeneic Wistar -bone marrow stromal cells at 24 h after ischemia and sacrificed at 28 days. Significant functional recovery was found in both cell-treated groups compared to stroke rats that did not receive BMSCs, but no difference was detected between allogeneic and syngeneic cell-treated rats. No evidence of T cell priming or humoral antibody production to marrow stromal cells was found in recipient rats after treatment with allogeneic cells. Similar numbers of Y-chromosome(+) cells were detected in the female rat brains in both groups. Significantly increased thickness of individual axons and myelin, and areas of the corpus callosum and the numbers of white matter bundles in the striatum were detected in the ischemic boundary zone of cell-treated rats compared to stroked rats. The areas of the contralateral corpus callosum significantly increased after cell treatment compared to normal rats. Processes of astrocytes remodeled from hypertrophic star-like to tadpole-like shape and oriented parallel to the ischemic regions after cell treatment. Axonal projections emanating from individual parenchymal neurons exhibited an overall orientation parallel to elongated radial processes of reactive astrocytes of the cell-treated rats. Allogeneic and syngeneic bone marrow stromal cell treatment after stroke in rats improved neurological recovery and enhanced reactive oligodendrocyte and astrocyte related axonal remodeling with no indication of immunologic sensitization in adult rat brain.

Maltsev, V. A. and A. I. Undrovinas (2006). "A multi-modal composition of the late Na⁺ current in human ventricular cardiomyocytes." *Cardiovasc Res* **69**(1): 116-27. [PDF Full-Text](#)

OBJECTIVE: We reported an ultraslow late Na⁺ current (INaL) in ventricular cardiomyocytes of human hearts. INaL has been implicated in regulation of action potential duration in normal hearts and repolarization abnormalities in failing hearts. We have also identified sodium channel (NaCh) gating modes including bursts (BM) and late scattered openings (LSM) that together comprise INaL; however, the contribution of these gating modes to Na⁺ current (INa) remains unknown. In the present study, the late NaCh activity was recorded, analyzed, and modeled for heterologously expressed NaCh, Nav1.5, and for the native NaCh of ventricular mid-myocardial cardiomyocytes from normal and failing hearts. METHODS AND RESULTS: We found that LSM gating was significantly slower in failing compared to normal myocytes and Nav1.5 (tau=474+/-10 vs. 299+/-9, and

229±12 ms, m±SEM; P<0.05, n=5-6). Total burst length of BM decreased with depolarization and was larger in failing compared to normal myocytes and Nav1.5. A complete INa decay was then numerically approximated as composed of NaCh populations operating in three gating modes described by separate Markov kinetic schemes: transient mode (TM), LSM, and BM. The populations of NaCh operating in each gating mode were estimated as 79.8% for TM, 20% for LSM, and 0.2% for BM, yielding an apparent four-exponential INa decay at -30 mV (maximum INa) (tau i approximately 0.4, 4, 50, and 500 ms). Whole-cell recordings confirmed the existence of all four predicted components. The model also predicted voltage and temperature dependence of INaL as well as INaL increase and slower decay in failing hearts and acceleration by amiodarone. CONCLUSIONS: The early phase of Na+ current decay (<40 ms) involves all three NaCh gating modes, the intermediate phase (from 40 to 300 ms) is produced by BM+LSM, although the contribution of BM decreases with depolarization, and ultra-late decay (>300 ms) is determined solely by LSM. The concept of multi-mode composition for INaL provides a new rationale for INaL modulation by factors such as voltage, temperature, pharmacological agents, and pathological conditions.

Meng, H., Z. Zhang, et al. (2006). "Biphasic effects of exogenous VEGF on VEGF expression of adult neural progenitors." *Neurosci Lett* **393**(2-3): 97-101. [PDF Full-Text](#)

Vascular endothelial growth factor (VEGF) regulates neurogenesis. The present study investigated the direct effect of VEGF on the enhancement of proliferation and differentiation of the adult mouse subventricular zone (SVZ) neural progenitors in vitro. A high dose (500 ng/ml) of VEGF significantly downregulated endogenous VEGF receptors 1 and 2, which was associated with significantly reduced neural progenitor cell proliferation and enhancement of neuronal differentiation. A low dose (50 ng/ml) of VEGF significantly upregulated endogenous VEGF receptors 1 and 2 but did not increase proliferation and differentiation. These data suggest that exogenous VEGF has a biphasic effect on the expression of endogenous VEGF receptors, and the high dose of VEGF enhances adult neural progenitor cell differentiation into neurons.

Morita, H., S. Khanal, et al. (2006). "Selective Matrix Metalloproteinase Inhibition Attenuates the Progression of Left Ventricular Dysfunction and Remodeling in Dogs with Chronic Heart Failure." *Am J Physiol Heart Circ Physiol*. [PDF Full-Text](#)

Background - Matrix metalloproteinases (MMPs) contribute to the progression of left ventricular (LV) dysfunction and remodeling associated with heart failure (HF). The present study examined the long-term effects of a selective MMP inhibitor, PG-530742 (PG), on the progression of LV dysfunction and remodeling in dogs with HF. Methods and Results - Chronic HF (LV ejection fraction [LVEF] ≤36%) was produced by multiple sequential intracoronary microembolizations in 24 dogs. Two weeks after the last embolization, dogs were randomized to 3 months of therapy with either high-dose PG (3.5mg/kg, n=8) (HD), low-dose PG (0.2mg/kg, n=8) (LD), or to a matched placebo (PL, n=8). PG has been shown to produce complete inhibition of MMPs 2, 3, 9, and -13, while sparing MMPs-1 and -7. Hemodynamic and echocardiographic measurements were made before and 3 months after initiating therapy. In PL dogs and in LD dogs, LVEF decreased significantly, and LV end-systolic volume (ESV) and LV end-diastolic volume (EDV) increased significantly during the 3-month follow-up period. Whereas, in HD dogs, EF increased from 36±1 % to 40±1 % (p=0.003), EDV and ESV decreased (59±4 vs. 57±4 ml, p=0.02, 38±2 vs. 34±2 ml, p=0.0001). Compared to controls, treatment with HD showed 30% reduction in replacement fibrosis, 29% reduction in interstitial fibrosis and 28% reduction in myocyte cross-sectional area. mRNA expression of selective MMPs was also reduced in LV tissue in HD-treated dogs but not LD-treated dogs. Conclusions - In dogs with moderate heart failure, long-term monotherapy with high dose selective MMP inhibitor, PG-53072, prevents LV remodeling and the progression of global LV dysfunction.

Nathanson, S. D., R. Slater, et al. (2006). "Her-2/neu expression in primary breast cancer with sentinel lymph node metastasis." *Ann Surg Oncol* **13**(2): 205-13. **Full-Text Not Available / [Click for Article Request Form](#)**

BACKGROUND: Amplification of the protein product of the HER-2/neu oncogene in primary breast cancer specimens is associated with an adverse prognosis. We hypothesized that overexpression of HER-2/neu would predict metastases to the sentinel lymph nodes (SLNs). METHODS: A retrospective review of a prospective nonrandomized evaluation of 1055 clinically node-negative breast cancer patients undergoing 1063 SLN biopsies was performed. HER-2/neu analysis was performed by immunohistochemistry and, in selected cases, by fluorescence in situ hybridization. Clinical, demographic, surgical, radiological, and pathologic data were analyzed by using generalized estimating equations logistic regression models. RESULTS: Two hundred thirty-two (23.6%) of 985 operations in which the SLN was found at operation resulted in positive nodes. In a multivariate analysis, size (P < .0001) and HER-2/neu overexpression (P = .026) were independent predictors of SLN metastasis.

CONCLUSIONS: Size is a known predictor of SLN metastasis in the modern SLN era, as it was in the pre-SLN eras. HER-2/neu was found to be significantly predictive of SLN metastasis in our study. We anticipate a future when even the relatively minor procedure of SLN biopsy might be avoided with the predictive information gained from studying the pathology and molecular markers of primary breast cancers.

Perrotta, A. L. (2006). "Re-treatment of chronic idiopathic thrombocytopenic purpura with rituximab: literature review." *Clin Appl Thromb Hemost* **12**(1): 97-100. **Full-Text Not Available** / [Click for Article Request Form](#)

The aim of this literature review was to identify from published reports, the characteristics and response to rituximab of nine patients with chronic idiopathic thrombocytopenic purpura who had been re-treated after responding to an initial course of therapy. The female/male ratio of re-treated patients was eight, suggesting selection or their suitability for treatment because the female/male ratio of 95 initially treated patients in all published reports between December 1998 and June 2003 was 2. Almost three times as many females responded to the first course of rituximab. All second responses, where recorded, were complete despite two previous partial responses and one minor response. The duration of the second response was at least as durable and more so than the first. Of the nine re-treated patients, the two failures had not undergone splenectomy, yet had achieved a complete response to the first course. All four patients who had previously responded to intravenous immunoglobulin responded to both the initial and subsequent course of rituximab. The influence of prior splenectomy, response to intravenous immunoglobulin, and distinctive patterns of time course until platelet response suggest that there might be different mechanisms of response to rituximab.

Pladevall, M., B. Singal, et al. (2006). "A single factor underlies the metabolic syndrome: a confirmatory factor analysis." *Diabetes Care* **29**(1): 113-22. [PDF Full-Text](#)

OBJECTIVE: Confirmatory factor analysis (CFA) was used to test the hypothesis that the components of the metabolic syndrome are manifestations of a single common factor. **RESEARCH DESIGN AND METHODS:** Three different datasets were used to test and validate the model. The Spanish and Mauritian studies included 207 men and 203 women and 1,411 men and 1,650 women, respectively. A third analytical dataset including 847 men was obtained from a previously published CFA of a U.S. population. The one-factor model included the metabolic syndrome core components (central obesity, insulin resistance, blood pressure, and lipid measurements). We also tested an expanded one-factor model that included uric acid and leptin levels. Finally, we used CFA to compare the goodness of fit of one-factor models with the fit of two previously published four-factor models. **RESULTS:** The simplest one-factor model showed the best goodness-of-fit indexes (comparative fit index 1, root mean-square error of approximation 0.00). Comparisons of one-factor with four-factor models in the three datasets favored the one-factor model structure. The selection of variables to represent the different metabolic syndrome components and model specification explained why previous exploratory and confirmatory factor analysis, respectively, failed to identify a single factor for the metabolic syndrome. **CONCLUSIONS:** These analyses support the current clinical definition of the metabolic syndrome, as well as the existence of a single factor that links all of the core components.

Qian, J. Y., A. Leung, et al. (2006). "PGE2 Stimulates Human Brain Natriuretic Peptide Expression via EP4 and p42/44 MAPK." *Am J Physiol Heart Circ Physiol*. [PDF Full-Text](#)

Brain natriuretic peptide (BNP) produced by cardiac myocytes has anti-fibrotic and anti-growth properties and is a marker of cardiac hypertrophy. We showed that prostaglandin E2 (PGE2) is the main prostaglandin produced in myocytes treated with pro-inflammatory stimuli and stimulates protein synthesis by binding to its EP4 receptor. We hypothesized that PGE2, acting through EP4, also regulates BNP gene expression. We transfected neonatal ventricular myocytes with a plasmid encoding the human BNP (hBNP) promoter driving expression of a luciferase reporter gene. PGE2 increased hBNP promoter activity 3.5-fold. An EP4 antagonist reduced the stimulatory effect of PGE2 but not an EP1 antagonist. Since EP4 signaling can involve adenylate cyclase, cAMP and protein kinase A (PKA), we tested the effect of H-89, a PKA inhibitor, on PGE2 stimulation of the hBNP promoter. 5 microM H-89 decreased PGE2 stimulation of BNP promoter activity by 100%. Since p42/44 MAPK mediates PGE2's effect on protein synthesis, we also examined MAPKs in the regulation of BNP promoter activity. PGE2 stimulation of the hBNP promoter was inhibited by a MEK1/2 inhibitor and a dominant-negative mutant of Raf, indicating that p42/44 MAPK was involved. In contrast, neither a p38 MAPK inhibitor nor a JNK inhibitor reduced the stimulatory effects of PGE2. Involvement of small GTPases was also studied. Dominant-negative Rap

inhibited PGE2 stimulation of the hBNP promoter, but dominant-negative Ras did not. We concluded that PGE2 stimulates the BNP promoter mainly via EP4, PKA, Rap and p42/44 MAPK.

Qiu, S., D. S. Rao, et al. (2006). "Differences in osteocyte and lacunar density between Black and White American women." *Bone* **38**(1): 130-5. [PDF Full-Text](#)

We examined the differences in osteocyte and lacunar density between Black and White women, using previously obtained iliac bone biopsies from 34 healthy Black women, aged 21-70 years, and 94 White women, aged 20-73 years. For each subject, the density of osteocytes (Ot.N/B.Ar), empty lacunae (EL.N/B.Ar), and total lacunae (Tt.L.N/B.Ar) and the proportion of osteocyte-occupied lacunae (Ot.N/Tt.L.N) were separately measured in whole trabeculae, superficial bone (<25 microm from the bone surface), and deep bone (>45 microm from the bone surface). Compared with White women, Black women had higher values for osteocytes, empty lacunae, and total lacunae and lower values for percent occupied lacunae in superficial bone and whole trabeculae ($P < 0.01$ to <0.001). In deep bone there were more osteocytes and total lacunae in Black women, but the other measurements did not differ significantly between the two groups. As in White women, there were fewer osteocytes and total lacunae and more empty lacunae in deep than in superficial bone. The regressions of osteocyte and total lacunar density on age were not significant in Black women, but postmenopausal Black women had fewer osteocytes than premenopausal Black women, and percent occupied lacunae declined significantly with age in whole trabeculae and deep bone, which could only have resulted from osteocyte death. In contrast to White women, there was no inverse relationship between bone formation rate and osteocyte density in superficial bone and the observed bone formation rate was lower than predicted by osteocyte density. We conclude the following: (1) Cancellous bone is made with more osteocytes in Black than in White women, most likely because of diminished apoptosis of osteoblasts; this could contribute to increased bone strength in Black women. (2) In Black women, as in White women, there are fewer osteocytes and total lacunae and more empty lacunae in deep than in superficial bone. (3) There was moderate age-related loss of osteocytes in deep bone in Black women, indicating that osteocyte density depends more on the age of the bone than on the age of the subject. (4) The higher osteocyte density in Black women was not responsible for their lower bone formation rate.

Roehrs, T., A. Kapke, et al. (2006). "Sex differences in the polysomnographic sleep of young adults: a community-based study." *Sleep Med* **7**(1): 49-53. [PDF Full-Text](#)

BACKGROUND AND PURPOSE: In small, clinical samples, men have reduced slow wave sleep compared to women. Given the higher prevalence of sleep-related breathing disturbance in men, this study assessed sex differences in sleep in a large, non-clinical sample of adults and controlled for primary sleep disorders. **PATIENTS AND METHODS:** Men and women, 31-40 years old, drawn from a longitudinal sample representative of southeast Michigan served as subjects. Each underwent a sleep study consisting of two consecutive 8-h nights of standard polysomnography (NPSG) and a multiple sleep latency test (MSLT) the intervening day. **RESULTS:** Of the 439 eligible participants, 292 (66.5%) agreed to spend two consecutive nights and the intervening day in the sleep laboratory. Standard polysomnograms that monitored respiration and leg movements were collected each night, and on the intervening day the MSLT was performed. Men had more sleep-related breathing disturbance than women. After adjusting for this higher prevalence of respiratory disturbance, men still had a lower mean sleep efficiency (i.e. increased wake time) and a higher percentage of stage 1 sleep. Men and women did not differ in most other sleep parameters and did not differ in level of daytime sleepiness on the MSLT. **CONCLUSIONS:** Sleep-related respiratory disturbance accounted for some of the sex differences in sleep. After correcting for respiratory disturbance, men still had lighter and less efficient sleep, but this was not associated with greater daytime sleepiness. Whether this reflects a sex difference in the functioning of the sleep homeostat will require further study.

Sheibani-Rad, S. and V. Velanovich (2006). "Effects of depression on the survival of pancreatic adenocarcinoma." *Pancreas* **32**(1): 58-61. [PDF Full-Text](#)

OBJECTIVES: Depression frequently predates the diagnosis of pancreatic adenocarcinoma. In other malignancies, depression has been shown to adversely affect survival. The purpose of this study was to assess whether survival after resection for pancreatic cancer is shortened by the pretreatment presence of depression. **METHODS:** A database of all patients diagnosed with pancreatic cancer was retrospectively reviewed for depression, resection, and chemotherapy and/or radiation therapy. A total of 258 patients were studied; 21% had depression, 19% had surgical resection of the tumor, and 42% were treated with chemotherapy and/or radiation therapy. Survival data was analyzed using Cox proportional hazard regression and life table analysis. **RESULTS:**

The median survival time for all depressed patients with pancreatic cancer was 5 months compared with 4 months for all nondepressed patients with pancreatic cancer ($P < 0.9$). There was no difference in stage, rate of surgical resection, rate of chemotherapy administration, or rate of radiation therapy use between depressed and nondepressed patients. **CONCLUSION:** Patients who had undergone surgical resection or chemotherapy and/or radiation therapy had longer survival times than those who did not. Depression, although common among patients with pancreatic cancer, does not affect survival.

Shen, L. H., Y. Li, et al. (2006). "Intracarotid transplantation of bone marrow stromal cells increases axon-myelin remodeling after stroke." *Neuroscience* **137**(2): 393-9. [PDF Full-Text](#)

The present study investigates the induction of axon and myelin remodeling as a possible mechanism by which treatment of stroke with bone marrow stromal cells improves neurological functional recovery. Adult male Wistar rats were subjected to 2 h of middle cerebral artery occlusion, followed by an injection of 2×10^6 rat bone marrow stromal cells or phosphate-buffered saline into the internal carotid artery 24 h later. Animals were killed at 28 days after stroke. Functional tests, histo- and immunohistochemical staining were performed. Significant functional recovery was found after bone marrow stromal cell administration in all the three tests performed (modified neurological severity score, adhesive-removal and corner tests). Bone marrow stromal cell treatment markedly increased vessel sprouting, synaptophysin expression and NG2 positive cell numbers and density in the cortical peri-infarct area. In bone marrow stromal cell-treated rats, the number of Ki-67 positive proliferating cells and oligodendrocyte precursor cells in the corpus callosum increased significantly in concert with the enhancement of the areas of the corpus callosum in both hemispheres. These results suggest that bone marrow stromal cells facilitate axonal sprouting and remyelination in the cortical ischemic boundary zone and corpus callosum, which may underlie neurological functional improvement caused by bone marrow stromal cell treatment.

Subramanian, B., A. Nakeff, et al. (2006). "A new paradigm for the development of anticancer agents from natural products." *J Exp Ther Oncol* **5**(3): 195-204. **Full-Text Not Available / [Click for Article Request Form](#)**

A novel pharmacology paradigm has been developed which quickly and efficiently moves prospective anticancer drugs from the discovery phase through pharmacology testing and into therapeutic trial assessment. Following discovery, the drug is first assessed in a clonogenic assay which determines the cytotoxic effect of different concentrations of the drug at 3 different exposure durations: 2h, 24h and continuous (168 h). Second, pharmacokinetic information is obtained in both plasma and tumor for the drug administered at the maximum tolerated dose given intravenously. The first study defines the time-concentration profile required to obtain a specific cell survival for the tumor cells; the second study determines the concentration-time profile that can be obtained in both plasma and tumor at the maximum tolerated dose of the drug. The integration of this information determines whether a successful therapeutic trial is possible. Only when a drug shows therapeutic efficacy is a proteomics-based mechanism of action study initiated. Two drugs have been assessed in this paradigm: salicortin and faspalyisin A.

Sundaram, S. and J. Ghosh (2006). "Expression of 5-oxoETE receptor in prostate cancer cells: critical role in survival." *Biochem Biophys Res Commun* **339**(1): 93-8. [PDF Full-Text](#)

Previously, we reported that metabolism of arachidonic acid through the 5-lipoxygenase (5-LOX) pathway plays an important role in the survival and growth of human prostate cancer cells. Inhibition of 5-LOX by pharmacological inhibitors triggers apoptosis in prostate cancer cells within hours of treatment, which is prevented by the metabolites of arachidonate 5-lipoxygenase, 5(S)-hydroxyeicosatetraenoic acid (5(S)-HETE), and its dehydrogenated derivative, 5-oxoeicosatetraenoic acid (5-oxoETE). These findings suggested that 5-lipoxygenase metabolites are critical survival factors of prostate cancer cells. However, molecular mechanisms by which 5(S)-HETE and its derivative 5-oxoETE exert their effects on prostate cancer cell survival are yet to be understood. Here, we report that human prostate cancer cells differentially express a G-protein-coupled 5-oxoETE receptor (5-oxoER) in them. Blocking expression of 5-oxoER by short-interfering RNA (siRNA) significantly reduced the viability of prostate cancer cells, suggesting that 5-oxoER is critical for prostate cancer cell survival, and that the 5-LOX metabolite, 5-oxoETE, controls survival of prostate cancer cells through its own G-protein-coupled receptor, 5-oxoER.

Tuchinda, C., H. W. Lim, et al. (2006). "Novel emerging sunscreen technologies." *Dermatol Clin* **24**(1): 105-17. **Full-Text Not Available** / [Click for Article Request Form](#)

Because of increases in the number of skin cancers diagnosed annually, adverse effects of ultraviolet (UV) rays are being recognized, and major public education programs have been undertaken concerning photoprotection, including the use of sunscreen. In daily life, UV exposure is unavoidable; therefore sunscreen should be used regularly. Development in sunscreen manufacturing has grown tremendously in the last decade. Sunscreen active ingredients now are incorporated into cosmetics products to minimize photoaging changes. With the advances in technologies, many new UV filters have been developed recently. These have improved efficacy and safety. This article reviews these new filters, along with regulatory issues in the United States.

Velanovich, V. (2006). "Case-control comparison of laparoscopic versus open distal pancreatectomy." *J Gastrointest Surg* **10**(1): 95-8. **Full-Text Not Available** / [Click for Article Request Form](#)

Laparoscopic distal pancreatectomy is becoming an increasingly used modality in the surgical treatment of pancreatic disease. The assumption is that this will lead to shorter hospitalization and faster recovery. However, actual comparative data between open and laparoscopic distal pancreatectomy is lacking. The purpose of this study is to compare these surgical procedures. All patients who underwent either laparoscopic or open distal pancreatectomy/splenectomy were reviewed. Fifteen patients underwent laparoscopic resection, whereas 41 underwent an open resection. The 15 laparoscopic patients were matched to 15 open patients for age, gender, and pancreatic pathology. Data gathered included length of stay, pancreatic leak, postoperative complications, and return to normal activity. Of the 15 laparoscopic patients, three were converted to open operations. Laparoscopic patients had a median length of stay of 5 days (range, 3-9) compared with 8 days (range, 6-23) for the open patients ($P = 0.02$). The pancreatic leak rate was 13% in each group. Overall postoperative complication rate was 20% in the laparoscopic group compared with 27% in the open group. Laparoscopic patients reported a return to normal activity in 3 weeks (range, 2-7) compared with 6 weeks (range, 4-10) for open patients ($P = 0.03$). Laparoscopic distal pancreatectomy/splenectomy does lead to shorter hospital stay and faster return to normal activity. Pancreatic leak rate and overall complication rate appear similar.

Velanovich, V. (2006). "Nonsurgical factors affecting symptomatic outcomes of antireflux surgery." *Dis Esophagus* **19**(1): 1-4. **Full-Text Not Available** / [Click for Article Request Form](#)

A small number of patients will have persistent or new symptoms after antireflux surgery for gastroesophageal reflux disease (GERD). Most of these symptoms are due to recurrent reflux or some complication or side-effect of the operation. However, a few of these patients will be symptomatic without objective findings to explain these symptoms. The purpose of this review is to highlight potential non-surgical factors that may proceed to a poor symptomatic outcome after antireflux surgery. These factors include underlying esophageal pathophysiology, issues related to chronic pain and pain perception, personality and psychoemotional disorders, functional esophageal and/or bowel disorders, and the nocebo phenomenon. Awareness of these other causes can lead to more appropriate treatments.

Velanovich, V., J. M. Morton, et al. (2006). "Analysis of the SAGES outcomes initiative cholecystectomy registry." *Surg Endosc* **20**(1): 43-50. [PDF Full-Text](#)

BACKGROUND: In 1999, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) introduced the SAGES Outcomes Initiative as a method for its members to use for tracking their own outcomes. This report provides a descriptive analysis of the cholecystectomy database. **METHODS:** The SAGES Outcome Initiative database was accessed for all gallbladder cases from September 1999 to February 2005. The data from the preoperative, intraoperative, and postoperative entries were summarized. These data are purely descriptive, and no statistical analysis was performed. **RESULTS:** The gallbladder registry contained 3,285 cases, with 2,005 follow-up cases. Most patients were employed women with some comorbidities who had elective surgery under general anesthesia. Most of the operating surgeons were attending surgeons and surgical assistants. Most of the patients had biliary colic, and symptoms were improved for more than 95% of the patients. More than 90% of the cases were managed laparoscopically, with a conversion rate of 3%. Biliary imaging was used in the vast majority of cases, with most shown to be normal. Intraoperative gallbladder perforation was common, with bile duct injury occurring

in 0.25% of cases. The most frequently cited postoperative event was wound infection, with most complications classified as class 1. More than 95% of the patients were able to return to work. **CONCLUSIONS:** The SAGES Outcomes Initiative database demonstrates that most participating SAGES members perform laparoscopic cholecystectomies themselves using intraoperative cholangiograms. Adverse outcomes are few, with most patients able to return to normal activity. Importantly, there were relatively few missing data points, implying that when surgeons enter data, the information is relatively complete.

Wong, H. K., A. J. Wilson, et al. (2006). "Increased expression of CTLA-4 in malignant T-cells from patients with mycosis fungoides -- cutaneous T cell lymphoma." *J Invest Dermatol* **126**(1): 212-9. [PDF Full-Text](#)

Mycosis fungoides (MF) is a low-grade lymphoma of cluster of differentiation (CD)4+, CD45RO+, cutaneous leukocyte antigen (CLA)+ T cells that homes to the skin. To understand the functional abnormalities in this disease, we study the regulation of cytotoxic T-lymphocyte antigen (CTLA)-4 in peripheral blood mononuclear cells (PBMCs) from patients with MF. CTLA-4 is a costimulatory molecule for T cells that functions in immunoregulation. Unlike the expression of CD28, which is expressed constitutively on T cells, CTLA-4 expression is highly regulated. In the analysis of PBMCs in MF, we found that CTLA-4 is stimulated by phorbol myristate acetate/A23187 to a greater level when compared to normals. This defect was seen in the dominant clones of T cells. The increased CTLA-4 expression was significant between normal and MF, with a correlation between higher expression of CTLA-4 and a higher grade of MF. In a patient whose disease progressed, the CTLA-4 level increased. The abnormal level of CTLA-4 was confirmed at both the transcription and translation levels. Although MF is associated with a Th2 bias, Th1 cytokines IL-2 and IFN-gamma enhanced CTLA-4 expression, while IL-4 did not. These findings reveal an abnormal regulation of CTLA-4 expression in MF and show that PBMCs from patients with MF have properties that are divergent from those of normal T cells.

Yang, J. J. and M. C. Yang (2006). "An improved procedure for gene selection from microarray experiments using false discovery rate criterion." *BMC Bioinformatics* **7**: 15. [PDF Full-Text](#)

BACKGROUND: A large number of genes usually show differential expressions in a microarray experiment with two types of tissues, and the p-values of a proper statistical test are often used to quantify the significance of these differences. The genes with small p-values are then picked as the genes responsible for the differences in the tissue RNA expressions. One key question is what should be the threshold to consider the p-values small. There is always a trade off between this threshold and the rate of false claims. Recent statistical literature shows that the false discovery rate (FDR) criterion is a powerful and reasonable criterion to pick those genes with differential expression. Moreover, the power of detection can be increased by knowing the number of non-differential expression genes. While this number is unknown in practice, there are methods to estimate it from data. The purpose of this paper is to present a new method of estimating this number and use it for the FDR procedure construction. **RESULTS:** A combination of test functions is used to estimate the number of differentially expressed genes. Simulation study shows that the proposed method has a higher power to detect these genes than other existing methods, while still keeping the FDR under control. The improvement can be substantial if the proportion of true differentially expressed genes is large. This procedure has also been tested with good results using a real dataset. **CONCLUSION:** For a given expected FDR, the method proposed in this paper has better power to pick genes that show differentiation in their expression than two other well known methods.

Zhang, L., Z. G. Zhang, et al. (2006). "Treatment of embolic stroke in rats with bortezomib and recombinant human tissue plasminogen activator." *Thromb Haemost* **95**(1): 166-73. **Full-Text Not Available / [Click for Article Request Form](#)**

Stroke elicits a progressive vascular dysfunction, which contributes to the evolution of brain injury. Thrombolysis with tissue plasminogen activator (tPA) promotes adverse vascular events that limit the therapeutic window of stroke to three hours. Proteasome inhibitors reduce vascular thrombotic and inflammatory events, and consequently protect vascular function. The present study evaluated the neuroprotective effect of bortezomib, a potent and selective inhibitor of the proteasome, alone and in combination with delayed thrombolytic therapy on a rat model of embolic focal cerebral ischemia. Treatment with bortezomib reduces adverse cerebrovascular events including secondary thrombosis, inflammatory responses, and blood brain barrier (BBB) disruption, and hence reduces infarct volume and neurological functional deficit when administered within 4 h after stroke onset. Combination of bortezomib and tPA extends the thrombolytic window for stroke to 6 h, which is associated with the

improvement of vascular patency and integrity. Real time RT-PCR of endothelial cells isolated by laser-capture microdissection from brain tissue and Western blot analysis showed that bortezomib upregulates endothelial nitric oxide synthase (eNOS) expression and blocks NF-kappaB activation. These results demonstrate that bortezomib promotes eNOS dependent vascular protection, and reduces NF-kappaB dependent vascular disruption, all of which may contribute to neuroprotection after stroke.