and those inducible into FVT and PVT/VF still had a risk of appropriate ICD therapy for spontaneous ventricular tachyarrhythmias of 5%/year, suggesting that the induction of MVT as the sole predictor of future arrhythmic events may be inadequate.

Cox Proportional Hazard Ratios

Variable	Hazard Ratio (HR)	95.0% Confidence Interval for HR		p Value
		Lower	Upper	
Noninducible vs PVT/VF	1.134	0.448	2.869	.791
FVT vs VF	0.588	0.209	1.651	.313
MVT vs VF	2.209	1.008	4.840	.048
Male sex	1.451	0.703	2.996	.314
Ischemic cardiomyopathy	0.629	0.363	1.090	.099
Ejection fraction %	0.977	0.960	0.994	.008
Primary vs secondary implant indication	1.906	0.662	1.814	.722

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DENDRITIC CELL–DEPENDENT INDUCTION OF BETA CELL–SPECIFIC REGULATORY T CELLS FOR SUPPRESSION OF AUTOIMMUNE DIABETES. K. Pothoven, K. Tarbell, H. Yang, R.M. Steinman, M. Suthanthiran, X. Luo, Northwestern University, Chicago, IL; New York, NY.

Background: Thymic-derived $CD25^+CD4^+$ regulatory T (Treg) cells have been found to play an important role in the pathogenesis of autoimmune diabetes. Challenges for their application as a potent immunomodulatory therapy are (1) the small size of the naturally occurring $CD25^+CD4^+$ Treg population and (2) the polyclonal nature of the existing $CD25^+CD4^+$ Treg cells. Here we describe a novel system of using dendritic cell (DC)-stimulated expansion in the presence of TGF-β1 for in vitro generation of beta cell–specific $CD25^+CD4^+$ T cells that are potent suppressors of autoimmune diabetes. **Material and Methods:** Naive BDC2.5/NOD $CD25^-CD4^+$ cells were obtained by cell sorting from pooled BDC2.5/NOD LNs. Splenic DCs from NOD mice were purified by CD11c-positive selection. Naive $CD25^-CD4^+$ T cells were either cultured with irradiated $CD11c^+$ DCs and BDC peptide (specific stimulation) or with anti-CD3 and anti-CD28 (nonspecific stimulation) for 7 days with or without TGF-β1, after which the $CD25^+$ T-cell fraction was purified and analyzed. **Results:** Purity of the BDC2.5/NOD $CD4^+CD25^-$ was routinely > 97%. At baseline, the $CD4^+CD25^-$ BDC T cells express minimal Foxp3 measured by FACS analysis and real-time PCR. Stimulation in the presence of TGF-β1 with either specific or nonspecific conditions leads to marked induction of Foxp3 expression to a level comparable to that seen in naturally occurring $CD25^+CD4^+$ Treg cells. This induction was not seen in the absence of TGF-β1. The induced $CD25^+CD4^+Foxp3^+$ BDC T cells generated with DCs plus BDC peptide (specific stimulation) maintained a high level of cell surface clonotype expression after stimulation and exert antigen-specific suppression in in vitro suppression assays. When cotransplanted with syngeneic islets in diabetic NOD mice, these cells significantly prolonged islet graft survival from a median of 12 to 46 days ($p = .0008$). When cotransferred with diabetogenic cells into NOD.scid recipients, theses cells significantly delayed the kinetics of diabetes onset ($p < .0001$). In contrast, $CD25^+CD4^+Foxp3^+$ BDC T cells induced with anti-CD3 and anti-CD28 (nonspecific stimulation) show lower levels of clonotype expression on cell surface and were unable to suppress BDC peptide–stimulated proliferation in vitro or protect islet grafts in vivo. **Conclusion:** Beta cell–specific BDC2.5 $CD25^+CD4^+$ cells with high levels of Foxp3 can be induced from naive BDC2.5 $CD4^+CD25^-$ cells by TGF-β1 in $CD11c^+$ DC-stimulated expansions. These cells harbor potent suppressive activity in an islet antigen–specific manner and suppress autoimmune diabetes.

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EFFECT OF THE S1P1 GENE KO ON LIPOPOLYSACCHARIDE-INDUCED MURINE ACUTE LUNG INJURY. S. Sammani, T. Mirzapoiazova, L. Moreno, R. Proia, C. Evenoski, J. Moitra, V. Natarajan, P. Singleton, J.G. Garcia, University of Chicago, Chicago, IL; Bethesda, MD.

Acute lung injury ALI/ARDS, a significant cause of morbidity and mortality, is characterized by a diffuse inflammatory parenchymal process with pulmonary EC vascular leak and alveolar flooding. This syndrome remains a significant cause of intensive care unit mortality, and more effective therapeutic interventions are needed. Our in vitro studies indicate that sphingosine 1-phosphate (S1P), a phospholipid angiogenic factor and a major barrier-protective product of platelets, produces endothelial cell barrier enhancement through ligation of the S1P family of receptors, especially S1P1, a G protein–coupled receptor expressed on vascular endothelial cells. Our previous data show that S1P, via S1P1, has impressive protective effects in both murine and canine models of ALI (McVerry et al, 2004). To better understand S1P receptors in barrier regulation, we examined LPS-induced ALI in S1P1 receptor heterozygous ($S1P1R^{+/-}$) mice. Our data demonstrate that the $S1P1\text{-}R^{+/-}$ mice exhibit increased barrier disruption compared with wild-type mice, reflected by an increase in protein (25%) and inflammatory cell count (20%) in bronchoalveolar lavage (BAL) fluid. To confirm the role of S1P1R on the S1P barrier-protective effect, we administered S1P (UM final blood concentration, iv) simultaneously with LPS (2.5 mg/kg) and evaluated lung inflammation 18 hours later. LPS-treated wild-type mice treated with S1P demonstrated profound reductions (> 50%) in BAL protein, whereas $S1P1^{+/-}$ mice similarly treated with S1P only exhibited only a ≈10% increase in BAL protein. In conclusion, our data using genetically engineered mice demonstrate a critical need for S1P1 receptors in vivo, particularly in conditions of endotoxemia.

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LIPID RAFT REGULATION OF HEPATOCYTE GROWTH FACTOR/C-MET-MEDIATED VASCULAR INTEGRITY: ROLE OF CD44, TIAM1/RAC1, DYNAMIN 2, AND CORTACTIN. P.A. Singleton, R. Salgia, L. Moreno-Vinasco, J. Moitra, S. Sammani, T. Mirzapoiazova, S.M. Dudek, J. Garcia, University of Chicago, Chicago, IL.

Endothelial cell (EC) barrier dysfunction results in increased vascular permeability, a feature of inflammation, tumor angiogenesis, atherosclerosis, and acute lung injury. Therefore, agents that protect vascular integrity have important therapeutic implications both in vivo and in vitro. We have previously shown that the binding of hepatocyte growth factor (HGF) to its cell surface receptor, c-Met, promotes Rac1-dependent increases in lung EC barrier function. Further examination of the regulatory mechanisms of HGF/c-Met-induced EC barrier enhancement revealed that HGF (25 ng/mL) promotes c-Met recruitment into specialized caveolin 1–enriched plasma membrane microdomains (lipid rafts). Abolishing lipid raft formation (MβCD) attenuated HGF-induced EC barrier enhancement. Within lipid rafts, HGF induced c-Met association with CD44 (a major glycoprotein receptor for hyaluronan). Silencing CD44 expression (siRNA) inhibited HGF-induced c-Met and Tiam1 (a Rac1 guanine nucleotide exchange factor) recruitment to lipid rafts, as well as the association of cortactin (an actin-binding regulatory protein) with dynamin 2 (a vesicular regulatory protein) within lipid raft structures. Silencing of either Tiam1 or dynamin 2 blocked HGF-induced Rac1 activation, cortactin recruitment to lipid rafts, and EC barrier enhancement. Silencing cortactin attenuated HGF-induced EC barrier regulation. Finally, HGF-mediated in vivo protection from lipopolysaccharide-induced pulmonary vascular hyperpermeability was inhibited in CD44 knockout mice. Taken together, these results suggest that lipid rafts are an essential regulator of HGF/c-Met-mediated barrier enhancement via a process involving CD44, Tiam1, Rac1, dynamin 2, and cortactin.

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GASTRIC CANCER PRESENTING AS SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD. P. Sircar, S. Shetty, B. Cheeran, E. Akinyemi, S. Niranjan, Coney Island Hospital, Brooklyn, NY.

Introduction: In clinical practice, it is not uncommon to come across cases of subacute combined degeneration of the spinal cord in patients with pernicious anemia. The commonest cause of cobalamin deficiency is due to inadequate absorption associated with pernicious anemia. Vitamin B_{12} deficiency is also associated with gastrectomy and autoimmune metaplastic atrophic gastritis. Although chronic atrophic gastritis can lead to an increased risk of intestinal-type gastric cancer and gastric carcinoid tumor, presumably owing to prolonged achlorhydria resulting from parietal cell loss, it is very unusual for neurologic complications to be the primary manifestation in a patient with gastric cancer. We present a rare case of gastric adenocarcinoma presenting initially with neurologic complications of B_{12} deficiency. **Case Report:** A 48-year-old Caucasian gentleman came to the hospital complaining of gait disturbance for 3 to 4 weeks. Symptoms began with paresthesia in the lower extremities and gradually progressed to a point where he was unable to walk without support. He also complained of early satiety and dyspepsia for a few months. His past medical history and family history were essentially unremarkable. He drank moderate amounts of alcohol on a regular basis and also smoked one pack of cigarettes a day, both for 20 years. On examination, his abdomen was benign, but he had significant neurologic findings. His mental status and cranial nerves were intact. Motor strength was 4/5 in both lower extremities and tone was increased bilaterally. Sensory examination revealed hypoesthesia in both lower extremities. Vibration and position sense were absent bilaterally. Plantars were equivocal. Initial laboratory data were consistent with macrocytic anemia (peripheral smear showing hypersegmented neutrophils), with hemoglobin of 9 g/dL and MCV of 110 fl. The vitamin B_{12} level was on the lower side (210 pg/mL), with an increased B_{12} binding capacity (1,637 pg/mL). Radiologic investigations of the spine were unremarkable, including MRI of the spine. The patient also underwent upper gastrointestinal endoscopy for evaluation of his dyspeptic symptoms, which revealed poorly differentiated gastric adenocarcinoma, well to moderately differentiated, in the background of acute and chronic gastritis. The specimen was negative for *Helicobacter pylori*. The patient was treated with vitamin B_{12}, and his neurologic symptoms improved dramatically. He also underwent partial gastrectomy and did well thereafter. **Discussion:** The lesion in subacute combined degeneration of spinal cord is specific for cobalamin deficiency and is proposed to be due to a defect in myelin formation of unknown mechanism. Symptoms begin with paresthesia and ataxia associated with loss of vibration and position sense and can progress to severe weakness, spasticity, clonus, paraplegia, and even fecal and urinary incontinence. Early treatment with vitamin B_{12} can prevent many complications and permanent disability. Patients with atrophic gastritis may have an increased risk of developing gastric or colorectal adenocarcinoma, but the data are not entirely conclusive. There are no set recommendations to screen these patients at a greater frequency than the general population. Nevertheless, it is prudent to periodically monitor stools in these patients for the presence of blood. As the above case represents, gastric carcinoma rarely have an unusual presentation like our patient had, and a high index of suspicion for it can potentially be lifesaving in an otherwise near-fatal diagnosis.

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METASTATIC MALIGNANT MELANOMA PRESENTING AS MASSIVE LOWER GASTROINTESTINAL BLEEDING. P. Sircar, D. Godkar, J. Balachandran, S. Niranjan, Coney Island Hospital, Brooklyn, NY.

Introduction: Malignant melanoma represents 1 to 3% of cancers in the United States, and its prevalence is steadily increasing. Metastatic melanoma of the small bowel is a pathologic entity that is infrequently reported, and antemortem diagnosis is made in only 1.5 to 4.4% of all patients with melanoma. Gastrointestinal metastases may manifest as mucosal or submucosal masses, serosal implants, or carcinomatosis. They arise more commonly in the mesentery or distal small bowel than the proximal gastrointestinal tract or colon. Rarely are these lesions symptomatic; sometimes patients present with pain, obstruction, and occult or overt gastrointestinal bleeding. We present an unusual case of metastatic malignant melanoma of the second part of the duodenum presenting as life-threatening gastrointestinal hemorrhage. **Case Report:** A 53-year-old Russian lady came to the emergency room after an episode of syncope. She also complained of progressively worsening shortness of breath and fatigue for a few months. Her past medical history was remarkable for a history of malignant melanoma of the skin diagnosed 3 years ago, for which she had received excisional surgery and had remained free of recurrence for 3 years. Physical examination was significant for extreme pallor and multiple pigmented skin lesions of variable sizes on the trunk and back. She was neurologically intact, and the abdomen was benign, but rectal examination revealed soft dark stool, strongly guaiac positive, without masses or lesions. Initial laboratory work revealed a hemoglobin of 5.7g/dL, with microcytic red cell indices (MCV 62.1 fl). Her electrolytes, liver function tests, and renal function tests were all within normal limits. Chest radiography revealed multiple parenchymal lesions bilaterally, and CT of the brain with intravenous contrast showed multiple lesions in the brain parenchyma without mass effect. The patient was transfused two units of packed red cells and underwent endoscopic studies to evaluate the cause of her profound anemia and was found to have a mass lesion at the second part of the duodenum. She underwent duodenoscopy with biopsy of the lesion, which revealed metastatic malignant melanoma (immunohistochemical stains showing S-100 and melan-A positive). Also, biopsy from the skin lesions at the back revealed malignant melanoma arising from compound nevus, with level III invasion, and a tumor thickness of 0.8 mm. The patient did not bleed any further from her

duodenal lesion but was not deemed to be a candidate for therapeutic resection of the lesion, owing to her widely metastatic disease. The patient underwent palliative radiotherapy for her brain lesions and was put on prophylactic steroids, but she went through a rapidly downhill course and succumbed to her disease a few weeks later. **Discussion:** Malignant melanoma has the propensity to metastasize widely. Most reported cases of gastrointestinal metastases are those of mucosal or submucosal masses, serosal implants, or carcinomatosis, the most common form being multiple submucosal implants growing intraluminally to cause intestinal obstruction. However, many of these lesions can also ulcerate, resulting in occult or overt gastrointestinal bleeding. Although patients with gastrointestinal tract metastases from melanoma carry a dismal prognosis, many such patients can have palliation of symptoms by surgical resection with minimum morbidity and mortality. It is therefore important for clinicians to make an accurate and timely diagnosis of the cause of gastrointestinal bleeding in such patients to prevent rapidly fatal outcomes.

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ADRENAL INSUFFICIENCY AS THE INITIAL PRESENTATION OF HIV DISEASE. P. Sircar, D. Godkar, J. Balachandran, S. Niranjan, Coney Island Hospital, Brooklyn, NY.

Introduction: Endocrine deficiencies, particularly functional abnormalities of the hypothalamopituitary-adrenal axis, are common in patients with human immunodeficiency virus (HIV) disease. In most cases, adrenal insufficiency, although present, is not enough to cause clinical symptoms. Few cases have been reported where adrenal insufficiency was the only complaint, or even more rarely, the presenting complaint of a patient with HIV disease, without evidence of any superimposed opportunistic infections. We present such a rare case, as we encountered at our hospital. **Case Report:** A 31-year-old African American male with no significant past medical history presented to the emergency room with 2 to 3 days of severe weakness, dizziness, fatigue, and vomiting. He was found to be hypotensive (blood pressure 70/50 mm Hg), the hypotension being refractory to fluid resuscitation. The patient was also hyperkalemic (potassium 5.5 mEq/L). Baseline cortisol was 5.1 mg/dL; stimulated value at the end of 1 hour with 250 μg of cosyntropin was 8.7 mg/dL. Extensive workup for sepsis was negative, and so were CMV, *Toxoplasma*, and cryptococcal antibody titers. CD4 count was 6/μL, and antibody to HIV-1 virus was positive, with a viral load of 450,000 copies/mL. The patient ultimately responded to stress doses of hydrocortisone(300 mg/d) during a hospital stay and was discharged on maintenance doses of 20 mg of hydrocortisone at am and 10 mg at pm. At 6 months of follow-up, the patient was doing well, and although it has not been possible to take him off steroids, he is currently on a maintenance dose of 10 mg at am and 5 mg at pm of hydrocortisone. **Discussion:** Various mechanisms have been proposed to explain the mechanism of adrenal insufficiency in HIV-positive individuals. More often than not, infective agents such as CMV, cryptococcus, human herpesvirus 8, and tuberculosis have been found to be the culprits. Many times, no definite etiology can be found, and such cases are usually attributed to HIV itself or some abnormal autoimmune process getting triggered in the face of generalized reduction in body immunity. Further research is needed to understand the true mechanism of adrenal insufficiency in such obscure cases. This rare case also serves as a reminder to clinicians to keep in mind the differential diagnosis of adrenal insufficiency as the presenting picture of acquired immune deficiency syndrome (AIDS), even when a background diagnosis of HIV positivity is absent.

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CHIRAL SEPARATION OF THE INOTROPIC AND CHRONOTROPIC ACTIONS OF DIGOXIN IN A CANINE MODEL. C. Spies, A. Gupta, D. Glock, J. Spoon, L. Williams, V. Ranade, J. Snell, J. Molnar, J.C. Somberg, Rush University, Chicago, IL; Lake Bluff, IL.

The digoxin molecule is chiral, having asymmetries at the C3 + C17 carbon centers that give rise to stereoscopic isomers. The actions of digoxin chiral isolates on cardiac conduction and contractility have been shown to differ in the guinea pig. Additional supplies of the chiral isolates were obtained through HPLC employing a cyclobond chiral column, separating digoxin into two distinct chromatographic peaks, each with a different retention time. The optical rotation of the two isolates were +17 and +3, respectively, with the same mass/change ratio (m/z) of 780, identical to racemate digoxin. The effects of the isolates were determined in 15 catheterized dogs anesthetized with isoflurane. The effects of the two chiral isolates were contrasted to digoxin for changes in HR, PR, and AH intervals, as well as left and right ventricular dp/dt. Digoxin and the isolates were infused at 1.5 μg/kg/min. Digoxin racemate caused a 15% slowing in HR at 45 minutes, a 15% increase in PR interval at 60 minutes, and a 20% increase in AH interval at 75 minutes. Dp/dt_r was increased by 20% at 15 minutes and 50% at 60 minutes, whereas dp/dt_L by 20% at 15 minutes and 50% at 105 minutes. Chiral isolate 1 failed to decrease HR or increase PR or AH intervals by 15%. Dp/dt_r was increased by 50% at 15 minutes and dp/dt_L by 20% at 15 minutes and 50% at 30 minutes. Isolate 2 slowed HR by 15% at 15 minutes and PR by 15% at 30 minutes, and AH decreased by 20% at 15 minutes, whereas dp/dt_r was increased by 20% at 45 minutes and dp/dt_L by 20% at 75 minutes; a 50% augmentation was not obtained. The contractility/conduction index (dose to 20% increase in dp/dt ÷ dose to 20% increase in AH interval) was 0.2 digoxin, < 0.125 chiral 1 and 3 for chiral 2. There is a marked difference between isolates 1 and 2 in AV conduction and contractile augmentation ($p < .001$). Digoxin can be chirally separated, with one isolate causing progressive AV conduction delay and the other isolate predominantly causing contractile augmentation.

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A CASE OF FULMINANT HEPATIC FAILURE TREATED WITH *N*-ACETYLCYSTEINE. J. Venkatesan, M. Soni, T. Schwartz, M. Bernstein, Coney Island Hospital, Brooklyn, NY.

Background: Fulminant hepatic failure is one of the most challenging gastrointestinal emergencies and encompasses a pattern of clinical symptoms and pathophysiologic responses associated with rapid arrest of normal hepatic function. Hyperacute hepatic failure usually presents with liver function abnormalities, coagulopathy, encephalopathy, and multisystem failure. This is a case report of hyperacute liver failure that presented with coagulopathy and an isolated elevation of aspartate aminotransferase and normal alanine aminotransferase. The etiology for liver failure is multifactorial. In our patient, the above presentation was attributed to therapeutic misadventure: acute acetaminophen toxicity in chronic alcoholics at a very low dose. The patient had improvement of symptoms and liver function after treatment with *N*-acetylcysteine. **Case Report:** A 51-year-old male with a past medical history of hypertension on ACE-I on and off was admitted with abdominal pain, nausea, and vomiting for 4 days. The patient took six 500 mg tablets of acetaminophen over 3 days' duration. In addition, he took enalapril 40 mg for his ill health. The patient gave a history of chronic alcohol abuse. Positive physical findings on admission include hypotension, which subsequently improved, conjunctival icterus, and tenderness over the right hypochondrium. Laboratory data showed creatinine 1.9, total bilirubin 5.7, direct bilirubin 2.7, AST 11,736, ALT 20, PT/INR 26.0/4.6, and alkaline phosphatase 141. Liver profile was repeated to check for error. Electrocardiogram showed normal sinus rhythm with left axis deviation. Abdominal sonogram showed distended gallbladder with moderate sludge, pericholecystic fluid. Acetaminophen level was 8.8. Differential diagnosis on admission included acetaminophen toxicity, shock liver, enalapril-related liver toxicity, alcoholic hepatitis, infectious hepatitis, autoimmune hepatitis, Wilson disease, and acute cholecystitis. The patient was started on intravenous *N*-acetylcysteine and vitamin K and was managed in intensive care with a plan for possible liver transplant. ANA; hepatitis A, B, C, D, and E; α_1-antitrypsin; ceruloplasmin; antimitochondrial Ab; and anti–smooth muscle Ab were negative. During the hospital course, the patient showed recovery in both symptoms and liver function tests. Isolated AST elevation noted for 24 hours and later ALT showed an increase followed by recovery of both AST and ALT. INR also improved. **Discussion:** A high index of suspicion of acetaminophen toxicity, even in low doses, is needed in patients with chronic alcohol abuse. The role of *N*-acetylcysteine is crucial in such patients and may be beneficial if the etiology of acute hepatic failure is unclear while investigations are being done. Isolated AST elevation was also an uncommon presentation in this patient.

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WHAT IS THE MECHANISM OF ENDOTHELIN 1'S EFFECT ON ISCHEMIC VENTRICULAR TACHYCARDIA? D. Xing, J.B. Martins, University of Iowa College of Medicine and VAMC, Iowa City, IA.

Background: Endothelin (ET), one of the most potent vasoconstrictors, is known to influence ventricular tachycardia (VT). The mechanism thought to be involved includes triggered activity (TA). We investigated effects of ET-1 and the ET-1A receptor blocker BQ123 in a canine model of focal and reentrant VT in a combined in vivo and in vitro study to test the hypothesis that focal VT and TA were selectively affected. **Methods:** Thirty-eight alpha-chloralose-anesthetized dogs with 1 to 3 hours of coronary artery occlusion were studied. Three-dimensional activation mapping identified the mechanism of VT. If VT was not inducible at baseline, incremental doses of ET-1 were given until the VT was induced. If VT was reproducibly induced at baseline, BQ123 was given (2.5 μg/kg, IV), and then induction was repeated. The effect of these agents on action potentials (APs), delayed and early afterdepolarizations (DADs and EADs), and TA measured from ischemic endocardium were studied in vitro by standard microelectrode techniques. **Results:** Of 15 dogs with no VT inducible, ET-1 (0.2 μg/kg, IV) produced sustained VT of mixed reentrant and focal origin in five dogs ($p < .05$ [*] vs saline alone). ET-1 did not change effective refractory period (ERP), pacing threshold, mean arterial pressure (MAP), or infarct size (37 ± 3% [SEM] to 39 ± 4%). Of 12 dogs with reproducible reentrant VT in control, only 1 had no VT inducible after saline. Of 11 dogs given BQ123, reentrant VT was prevented in 4 of 6*; surface ECG and intracardiac T-wave alternans was blocked in all experiments. Zero of five dogs with focal origin of VT was prevented. BQ123 did not change ERP, threshold, MAP, or infarct size. In vitro APs were not substantially changed by ET-1 until rapid pacing produced AP alternans facilitated by ET-1 in 8 of 15 tissues; however, ET-1 (10-10-10-8 M) did not facilitate EADs, DADs, or TA. **Conclusion:** ET-1 promotes focal and reentrant VT under conditions of myocardial ischemia; however, in vitro tissues do not show TA as we expected. The specific ET-1A receptor blocker BQ123 significantly blocked only reentrant VT. Endothelin plays a major role in reentrant VTs in the dog model of myocardial ischemia probably by promoting AP alternans.

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DYAMIC CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING PHARMACODYNAMIC STUDY OF SORAFENIB IN METASTATIC RENAL CELL CARCINOMA: PRELIMINARY RESULTS OF A RANDOMIZED, PHASE II TRIAL. C. Yang, O. Hahn, M. Medved, G. Karczmar, E. Kistner, T. Karrison, B. Manchen, M. Mitchell, M. Ratain, W.M. Stadler, University of Chicago, Chicago, IL.

Background: Sorafenib is an oral antiangiogenic agent with activity in renal cell cancer (RCC). We conducted a randomized, placebo-controlled trial to investigate if dynamic contrast-enhanced MRI (DCE-MRI) is a pharmacodynamic (PD) marker for sorafenib. **Method:** Patients were randomized in a double-blind manner to placebo, 200 mg bid sorafenib, or 400 mg bid sorafenib. DCE-MRI was performed at baseline and after 28 days of therapy, at which time placebo patients were rerandomized to low- or standard-dose sorafenib. RECIST-based progression was determined by CT scans performed every 12 weeks. DCE-MRI parameters, including the area under the contrast concentration versus time curve for 90 seconds after contrast injection (IAUC90), were calculated for a tumor region of interest in a blinded manner. Plasma steady-state sorafenib concentrations were obtained on day 28. **Results:** To date, 43 of a planned 66 patients have been enrolled, and 34 have undergone two protocol-defined MRIs, of which 33 are technically evaluable for the study end points. All analyses were conducted using the log ratio of the mean IAUC90 at 4 weeks versus the mean at baseline. The estimates of the log ratio and the corresponding standard deviations in the placebo, 200 mg, and 400 mg cohorts were 0.032 (± 0.235), −0.066 (± 0.138), and −0.281 (± 0.430), respectively ($p = .0156$ for linear trend between dose and the log ratio of IAUC90). These correspond to relative changes of +3%, −6%, and −24% in the placebo, 200 mg, and 400 mg cohorts, respectively. In the 27 patients with available plasma sorafenib levels, change in IAUC90 did not correlate with sorafenib steady-state levels ($p = .7507$). Current median follow-up is 20 weeks. Using a Cox proportional hazards model, IAUC90 change is not a significant predictor of progression-free survival ($p = .229$). The mean arterial pressure increased with sorafenib dose, but no correlation with IAUC90 change was detected ($p = .445$). **Conclusions:** DCE-MRI is a PD marker for sorafenib, and intrapatient variability is similar to previous reports, but the magnitude of effect in this prospective blinded study is less than previously reported. Ongoing analyses seek to assess the value of other DCE-MRI markers, such as Ktrans, and to correlate the DCE-MRI markers with more mature clinical follow-up data.

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SYNERGISTIC ENHANCEMENT OF BREAST CANCER CHEMOTHERAPY BY PAR1 PEPDUCINS. E.J. Yang, A. Agarwal, N. Nguyen, A. Kuliopulos, L. Covic, Tufts University, Boston, MA.

Protease-activated receptor 1 (PAR1) belongs to a unique family of G protein–coupled receptors that carry their own tethered ligand at the extracellular domain. Upon proteolytic cleavage, the ligand is exposed and is allowed to intramolecularly self-activate, triggering a cascade of signaling events leading to changes in cell shape, proliferation, migration, secretion, adhesion, and gene transcription. PAR1 is identified as an oncogene, and its expression is implicated in the development and metastasis of cancers of the breast, ovary, prostate, lung, pancreas, colon, and skin. The level of PAR1 expression correlates