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Abstract Book

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Oral Presentations

8:15 am

Pioglitazone attenuates alcohol-induced alveolar macrophage oxidative stress by down-regulating NADPH oxidases

Yeligar SM, Harris FL, Brown LAS, and Hart CM

Alcohol abuse increases risk of respiratory infections through impaired lung immunity mediated by enhanced alveolar macrophage (AM) oxidative stress, which results in phagocytic dysfunction. Peroxisome proliferator-activated receptor (PPAR)g ligands reduce lung oxidative stress through down-regulation of NADPH oxidases (Nox) 1, 2 and 4. We hypothesized that treatment with pioglitazone (PIO), a PPARg ligand, would attenuate alcohol-induced AM dysfunction by down-regulating Noxes and subsequently decreasing AM oxidative stress. AMs were obtained from the bronchoalveolar lavage (BAL) fluid of C57BL/6J mice fed \pm ethanol (20% w/v) in the drinking water for 12 wks and treated \pm 10 mg/kg/day PIO during week 12. In parallel, MH-S cells, a mouse AM cell line, were treated \pm 0.08% ethanol for 3 d \pm 10 μ M PIO for 1 d. mRNA and protein levels of Nox1, Nox2, and Nox4 were assessed by qRT-PCR and western blot, respectively. Oxidative stress was measured with DCFH-DA and Amplex Red assays, and mitochondrial bioenergetics was determined using Seahorse Bioanalyzer mitochondrial stress testing. AM function was evaluated by phagocytosis assay (*S. aureus* internalization). In vivo and in vitro, ethanol: 1) increased Nox1, Nox2, and Nox4 expression, 2) enhanced oxidative stress, 3) decreased mitochondrial oxygen consumption rate, and 4) impaired phagocytic capacity. PIO treatment reversed these ethanol-induced AM derangements. Our studies suggest PIO as a clinically relevant intervention that will ameliorate alcohol-induced AM dysfunction by down-regulating Nox expression despite continued alcohol ingestion.

8:30 am

The tale of two neglected tropical infections: using GIS to assess the spatial and temporal overlap of schistosomiasis and leprosy in a region of Minas Gerais, Brazil

Fairley JF, Phillips DA, Ferreira JA, Ansh D, Herica S, de Alcantara MH, de Filippis T, Kitron U

Background: Leprosy remains a problem in highly endemic areas, with Brazil carrying the second highest burden of disease globally. Helminth coinfection may increase the likelihood of the most infectious form of the disease, thus increasing transmission. This project presents the first-known analysis of the geospatial and temporal overlap of leprosy and *Schistosoma mansoni* infection in Brazil.

Methods: Data on new cases of leprosy and schistosomiasis were retrieved from the Brazilian national notifiable disease surveillance system (SINAN) for the years 2007-2014 for 7 municipalities in or near Vespasiano, Minas Gerais. Demographic data were tabulated and cases were mapped to

the neighborhood level using ArcGIS (v10.3.1). Data were then analyzed for temporal and spatial associations.

Results: 139 cases of leprosy and 200 cases of *S. mansoni* infection were reported. Maps demonstrate pockets of increased overlap of *M. leprae* and schistosomiasis. In the largest municipality, the relative risk for detecting leprosy in a neighborhood with reported schistosomiasis vs. those without was 6.29 (95% CI 2.11 – 18.76), adjusted for population density and purchasing power. The incidence of both diseases was highest from 2009-2011, peaking in 2011.

Discussion: These data suggest an association between *S. mansoni* and *M. leprae* infection that is independent of population and purchasing power and support the hypothesis that co-infection with schistosomiasis may increase the reservoir of *M. leprae* in some areas. Further work will investigate the epidemiologic and immunologic factors of co-infections, results of which could provide the foundation for more integrated control efforts for these neglected infections.

8:45 am

Satellite cells are the major source of the receptor for advanced glycation end products and play a role in collateral growth

Hansen LM, Lyle A, Joseph G, Weiss D, Taylor WR

Peripheral artery disease is major health problem that can lead to complications. While the growth of collateral vessels helps restore blood flow and improve outcomes, collateral formation is a complex process that involves numerous signaling molecules as well as cell proliferation and migration. The receptor for advanced glycation end products (RAGE) is thought to play a detrimental role in the process; however, the cellular source and its role are not fully understood. The central hypothesis of this study is that satellite cells are a major source of RAGE in ischemic regions and play a signaling role in collateral growth. Using the hind limb ischemia (HLI) model of collateral growth, RAGE expression was increased in the ischemic versus non-ischemic leg. However, the infusion of PEG-Catalase to decrease hydrogen peroxide (H_2O_2) significantly blunted the increase. These results suggest that RAGE expression is mediated by H_2O_2 . Histology and satellite cells isolated from the legs following HLI showed satellite cells in the ischemic leg had increased RAGE expression while satellite cells in the non-ischemic leg had almost no expression, and RAGE expression is enriched in satellite cells compared to the non-satellite cell fraction. Both primary cell lines and cells extracted from the leg following HLI show expression of several proteins important in collateral formation including VEGF, MCP-1, and osteopontin. Thus in addition to being a major source of RAGE in the ischemic limb, satellite cells may also serve as a novel source of paracrine factors regulating collateral growth.

9:00 am

Hospitalization costs, resource hospitalization, and clinical outcome in patients undergoing CABG surgery: Intensive vs. conservative glycemetic control

Cardona SD, Smiley DD, Weaver J, Register K, Peng L, Pasquel FJ, Umpierrez GE

GLUCO-CABG trial reported that intensive control (IC)-BG: 100-140 mg/dL in the ICU vs conservative control (CC)-BG: 141-180 mg/dL did not reduce hospital complications including infections, acute respiratory or renal failure, major cardiovascular events, and death (42% vs. 52%, p=0.08) in hyperglycemic patients undergoing CABG surgery. Financial impact of this intervention, however, is unknown. We conducted a cost analysis to compare hospitalization costs using 2011-2013 cost-change ratios from Center for Medicare & Medicaid Services, as well as resource utilization and hospital complications in CABG patients receiving IC vs CC. 288 patients (IC: 144, CC: 144) had data for analysis. Mean age was 64.2±9.5 with 50% prevalence of diabetes in each group. Hospitalization costs in the IC group were lower: \$39.4 K compared to \$42.2K in the CC group (p=0.043), with cost savings of \$2,699 (95% CI: \$557-6,750). Resource utilization was higher in the CC group for radiology (20 vs 15, p=0.001), laboratory (248 vs 213, p=0.018), consult service (14 vs 9, p=0.017), and ICU use (3 vs 2, p=0.013) which resulted in higher total resource costs compared to the IC group (\$16.3K vs \$14.2K, p=0.006). CC group had more complications (52% vs 42%, p=0.076) compared to IC group. A multivariate analysis adjusted for treatment group, DM status and complications suggested the cost benefit of IC is due to reduced complication rate. In summary, intensive glucose control, compared to conservative control in ICU patients that underwent CABG procedures is associated with fewer complications resulting in significantly lower hospitalization costs and resource utilization.

10:15 am

Autoantibodies utilizing the immunoglobulin heavy chain variable region gene 4-34 (VH4-34) exhibit autoreactivity towards, and potential competition with galectins within Systemic Lupus Erythematosus (SLE)

Cashman KS, Chida AS, Sanz I.

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by the propagation of autoreactive B cell populations leading to the production of pathogenic antibodies directed towards self-antigens. However, this autoreactive B cell expansion within SLE patients is not uniform suggesting specific antigen selection and skewing the antibody repertoire. One such expansion is in antibodies encoded by the VH4-34 gene. This antibody family has been shown to enrich in binding to autoantigens such as dsDNA, and can be uniquely examined due to the expression of the idiotope specific for the 9G4 idiotypic antibody. A secreted glycan binding protein family (the galectins), is also increased within SLE patients and has been shown to bind to many of the same antigenic targets as 9G4+ antibodies. The purpose of this study is to understand the interaction between VH4-34 encoded Ig and galectin binding

and/or competition in context of the pathogenesis of SLE. The VH4-34 gene segment encoded a significant portion of the total galectin-3 autoAbs (50% of SLE patients were anti-Galectin-3 positive). Galectin-1 and galectin-9 autoAb titers showed no such relationship however there was 9G4 autoreactivity in 6.25% and 18.75% of SLE patients respectively, and no 9G4+ anti-galectin reactivity within the HC group. There was no correlation of anti-galectin autoAbs and disease activity (SLEDAI). Additionally, two mAb derived from a pool of 20 (6.67%) 9G4+ mAbs and their site directed mutants were cross-reactive between both galectin-1 and galectin-9. This interaction was also determined to be a result of the CDR3, not the 9G4 idiotope.

10:30 am

Role of miR-155 in acute oscillatory shear stress-mediated oxidative stress, inflammation and endothelial dysfunction

Mohamed J, Elms S, Rooney K, Sutliff R, Searles C Shear stress forces play an integral role in dictating the endothelial cell (EC) response to changes in blood flow, proinflammatory response and development of atherosclerosis. Previously, our group has identified EC microRNA-155 (miR-155) as one of the key signature dysregulated miRNAs in models of low magnitude oscillatory shear stress (OSS) in vitro and in vasculature. We hypothesize that miR155 plays a direct role in early EC response to acute changes in vascular OSS. 12-week old C57B/6J mice were subjected to abdominal aortic coarctation (AAC), a unique model of acute induction of OSS, for 3 days and segments of acute OSS were compared with unidirectional shear stress (USS) segments of thoracic aorta. Acute OSS resulted in down regulation of EC miR155 expression that was associated with impaired endothelial dependent relaxation and differential contractile response to phenylephrine. Enface immunohistochemical staining showed increased expression of EC Angiotensin II receptor 1 (ATR1) and nitric oxide synthase (eNOS), along with increased levels of reactive oxygen species (ROS) and nitrotyrosine (NY) formation in OSS segments compared with USS. In parallel, RhoA and Myosin light chain kinase (MYLK), other known targets of miR-155-mediated EC cytoskeleton organization, were also upregulated in OSS segments compared with USS. Together, our studies shed light on the early changes in EC response to acute systemic blood flow changes and downregulation of EC miR-155, including; oxidative/inflammatory stress, EC dysfunction and cytoskeletal changes. Despite the early upregulation of eNOS, it could potentially synergize with increased AT1R expression on EC oxidative/inflammatory stress and associated dysfunction.

10:45 am

The effect of discordant and unrelated chronic conditions on the association of multimorbidity with mortality and healthcare utilization in chronic kidney disease

Bowling CB, Plantinga L, Phillips LS, McClellan W, Echt K, Chumbler N, McGwin G, Vandenberg A, Allman RM, Johnson II TM

Background: Chronic kidney disease (CKD) almost universally occurs in individuals with other medical problems. However, few studies have described CKD-related multimorbidity using a

framework that identifies chronic conditions as concordant (having overlap in treatment goals), discordant (having opposing treatment recommendations) or unrelated (having no overlap, but contributing to complexity via different resource requirements).

Methods: We assembled a national retrospective cohort of 821,334 Veterans Affairs patients with incident CKD defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m² for at least 3 months between 1/1/2005 and 12/31/2008 excluding prevalent CKD. We determined the associations of number of chronic conditions (1, 2, 3, 4, 5, 6 or more) stratified by the presence of one or more discordant/unrelated conditions with mortality, hospitalizations and emergency department (ED) visits.

Results: Higher risks of death, hospitalization and ED visits were associated with higher number of chronic conditions, among those with and without discordant/unrelated conditions. However, the magnitudes of the associations were consistently larger when at least one discordant/unrelated condition was present. For example, compared to patients with one concordant condition, patients with six or more concordant conditions had an age-, race- and sex- adjusted hazard ratio (HR) for mortality of 1.72 (95% CI 1.64 – 1.80) whereas those with six or more conditions, at least one of which was discordant/unrelated had a HR of 2.05 (2.01 – 2.09) (p-interaction < 0.001).

Conclusions and Relevance: The presence of one or more discordant/unrelated conditions was associated with increased risk for adverse health outcomes, beyond the effect of multimorbidity.

11:00 am

Gut microbial dysbiosis and increased plasma saturated fatty acids induced by Western diet lead synergistically to enteric neuronal degeneration and intestinal dysmotility

Reichardt F, Nezami BG, Tabatabavakili S, Liang B, Uppal K, Gewirtz A, Jones D, Srinivasan S

Introduction: High-fat diets are associated with colonic motility disorders inducing constipation and nitrergic myenteric neuronal loss in the proximal colon. The gut microbiota alteration and the increased plasma free fatty acids (FFA) also observed with fatty diets are hypothesized to be involved in the pathophysiology of these disorders. We used a Western-diet (WD, 35% Cal from fat) containing excessive saturated fat such as palmitate vs. a regular diet RD (16.9% Cal from fat) to understand the underlying mechanisms of high-fat diet induced neurodegeneration.

Methods: C57Bl/6 mice were fed a WD or RD for 3, 6, 9 and 12 weeks. Gut microbiota dysbiosis was investigated in the feces after 6 weeks by high-resolution metabolomics analysis. Colonic motility, nitrergic myenteric neurons quantifications and plasma FFA measurements were assessed at each time point. **Results:** Compared to controls, WD mice were heavier at 6 (+41%, P<0.05) and 12 weeks (+87%, P<0.001). Fecal analysis showed an increase of metabolites from gram-negative bacteria (such as diaminopimelic acid) suggesting dysbiosis in WD fed-

mice, fed for 6 weeks. These mice also had an increased FFA (+19%, P<0.05). A reduced number of nitrergic myenteric neurons was observed in the proximal colon after 9 (-41%, P<0.05) and 12 weeks (-51%, P<0.001) of WD where it was associated to a delayed colonic transit (+196%, P<0.05). Finally, in vitro treatment with palmitate and LPS synergistically-induced loss of cultured enteric neurons.

Conclusion: We demonstrate that the WD-induced loss of the nitrergic myenteric neurons is due to both gut microbial dysbiosis and the plasma FFA increase, and contributes to the delayed colonic transit.

2:00 pm

Quantified redox proteomic and metabolomic effects of switching peroxidase-derived oxidants in human lung epithelial cells

Chandler JD, Tran V, Orr ML, Liu K, Banton SA, Go YM, Jones DP

Inflammation results in production of hypochlorous (HOCl), hypobromous (HOBr) and hypothiocyanous (HOSCN) acids by myeloperoxidase in vivo. These potent 2-electron oxidants differ in reactivity and selectivity in spite of their superficial similarities; e.g., methionine (Met) is rapidly oxidized by HOCl and HOBr, but HOSCN reacts preferentially with cysteine (Cys). Therefore, we used mass spectrometry (MS) and molecular methods to quantify oxidant-specific redox proteomic and metabolomic effects upon exposure of BEAS-2B lung epithelial cells to equal doses of aforementioned oxidants and H₂O₂, their metabolic precursor. Early glutathione (GSH) oxidation by HOSCN was most significant, followed by H₂O₂, HOBr and HOCl (ANOVA p=0.0007). However, by 24 h, HOCl, HOBr and H₂O₂ had caused cytotoxicity but HOSCN did not. HOSCN decreased oxidation of biosynthesis enzymes (e.g., methionine adenosyltransferase C104, adenosylhomocysteinase C195) and metabolic precursors (e.g., S-adenosyl Met and glutamate) of GSH, consistent with 3.0-fold increase in GSH abundance (p<0.0001). HOSCN also oxidized many protein Cys, including phosphatases (PP2A, C13; PP2C, C84), cytoskeletal proteins (profilin C128, cofilin C139) and glycolytic enzymes (ALDOA, C232; GPI, C443), and maximally perturbed 581 metabolites. In contrast, HOCl and HOBr caused more rapid disruption, maximally perturbing 1068 and 995 metabolites (respectively) after 24 h. HOCl and HOBr potentially abolished Met, increasing Met sulfoxide (MetO) abundance >10³-fold (p<0.0001). Targeted MS2 revealed Met(S)O:Met(R)O stereoisomer ratio was oxidant-dependent, with HOCl and HOBr favoring higher relative Met(S)O (ratio of 1.47 vs. 1.17 for control; p<0.05). This analysis shows that oxidants with superficial similarities differ in redox proteomic and metabolomic targets in lung epithelia.

2:15 pm

Immunology of HIV-induced bone loss

Titanji K, Vikulina T, Vunnavu A, Sheth A, Easley K, Ofotokun I, Weitzmann MN

HIV induces significant bone loss that is exacerbated by Antiretroviral therapy (ART), culminating a 9-fold higher fracture

risk in the aging HIV/AIDS population. Bone loss ensues when osteoclastic bone resorption outpaces osteoblastic bone formation. Bone resorption is induced by binding of RANK Ligand (RANKL) to its receptor (RANK) on osteoclast precursors. Osteoprotegerin (OPG) is a decoy receptor for RANKL and suppresses its activity. Human B cells are a significant basal source of bone-protective OPG, while activated T and B cells secrete RANKL, driving bone loss in inflammatory conditions. We investigated a possible immunocentric basis for HIV-induced bone loss in an animal model of HIV infection and antiretroviral therapy (ART)-naïve HIV-infected individuals. We reported a significant decline in B cell OPG, concurrent with a significant increase in B cell RANKL. This inversion in RANKL/OPG ratio correlated with bone loss in HIV infection. Interleukin-4 (IL-4) is a key CD4+ T cell cytokine that potently regulates B cells. We now show for the first time that IL-4 is a potent inducer of OPG and suppressor of RANKL in both human and murine B cells. A decline in IL-4 could explain the HIV-induced alterations in B cell OPG and RANKL. We documented a profound decline in IL-4 production in HIV-infected patients that significantly correlated with bone resorption and did not normalize despite 4 years of ART. In conclusion our data suggest that IL-4 decline in HIV infection promotes bone loss, even in the context of otherwise successful ART.

3:15 pm

Association between baseline neutrophil-lymphocyte and platelet-lymphocyte ratio with outcomes after transcatheter aortic valve replacement

Condado JF, Junpaparp P, Thourani V, Devireddy C, Leshnowar B, Mavromatis K, Sarin EL, Stewart J, Guyton R, Forcillo J, Patel A, Block PC, Babaliarios V

Background: Baseline neutrophil-lymphocyte Ratio (NLR) and platelet-lymphocyte ratio (PLR) are associated with cardiovascular disease severity and poor outcomes after coronary artery bypass grafting. We aimed to determine the predictive role of NLR and PLR in outcomes after transcatheter aortic valve replacement (TAVR)

Methods: We retrospectively reviewed 520 patients with severe aortic stenosis that underwent balloon-expandable TAVR at our institution between 11/2007 and 12/2014 and had preprocedural complete blood count (CBC) with differential. The association between both NLR and PLR with baseline characteristics and 30-day outcomes was determined. For statistical power, the composite early safety outcome (defined by VARC-2 criteria as 30-day: mortality, major vascular complication, life-threatening bleeding, postoperative permanent stroke, and postoperative renal failure) was used.

Results: We found an association between NLR and history of previous valve surgery ($p < 0.01$), STS score ($p = 0.01$), left ventricular ejection fractions ($p = 0.05$), aortic valve mean gradient ($p = 0.05$), creatinine ($p = 0.05$) and hemoglobin ($p = 0.05$); and an association between PLR and age ($p = 0.02$), gender ($p = 0.04$), body mass index ($p = 0.01$), diabetes ($p = 0.04$), STS score ($p = 0.02$), Creatinine ($p = 0.03$), and hemoglobin ($p < 0.01$). Both the NLR and PLR were associated with the occurrence of the

early safety outcome after TAVR (NLR: OR 1.29, CI 1.04-1.59; PLR: OR 1.29, CI 1.03-1.62).

Conclusions: In high surgical risk patients with severe aortic stenosis, baseline NLR and PLR correlate well with underlying surgical risk (STS score) and post-procedural complications after TAVR. Suggesting that the NLR and PLR can be used to stratified pre-TAVR risk in these patients.

3:30 pm

Dietary modulation of intestinal epithelial permeability promotes non-alcoholic steatohepatitis progression in mice with defective intestinal epithelial barrier

Rahman K, Thorn NE, Desai C, Iyer SS, Kumar P, Smith T, Neish AS, Nusrat A, Parkos CA, Anania FA

Background & Aims: Although epidemiological evidence implicates intestinal barrier dysfunction in the pathogenesis of non-alcoholic steatohepatitis (NASH), the precise mechanisms underlying this phenomenon remain poorly understood. Here we investigated this question utilizing junctional adhesion molecule A deficient (JAM-A^{-/-}) mice, which have a defect in intestinal epithelial permeability (IEP).

Methods: Male C57BL/6 (WT) or JAM-A^{-/-} mice were fed a normal diet (ND) or a high fat, high fructose and high cholesterol diet (HFCD) for 8 weeks. Liver and intestinal tissue were subjected to histologic, RT-qPCR, and flow cytometric analyses. IEP was assessed by in vivo FITC-Dextran permeability. Gut microbiota were analyzed using 16S rRNA sequencing.

Results: JAM-A^{-/-} mice fed a HFCD developed severe histopathological features of NASH including steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis; while only modest steatosis was observed in the WT controls. Liver injury in the HFCD-fed JAM-A^{-/-} mice was associated with significantly increased mucosal inflammation, tight junction disruption, and increased IEP to bacterial endotoxins relative to WT controls. Examination of gut microbial composition revealed a striking increase in pro-inflammatory microbial taxa in HFCD-fed JAM-A^{-/-} mice. Notably, oral antibiotic treatment attenuated mucosal inflammation and restored normal liver histology.

Conclusions: The data strongly support a mechanistic link between diet, intestinal epithelial barrier, microbial dysbiosis and NASH pathogenesis. Our findings demonstrate that defective IEP is essential for HFCD-induced NASH development. Together, these findings indicate that restoration of intestinal barrier integrity and manipulation of gut microbiota may be of therapeutic value in NASH.

Poster Presentations

In alphabetical order by presenting author.
Presenting author underlined.

Poster number and session listed above abstract.

Morning poster session 9:15 – 10:00 AM

Afternoon poster session 2:30 – 3:15 PM

#1 (morning session)

Incidence of major complications during outpatient colonoscopy for colon cancer screening

Abdeljawad K, Qayed E, Shroff S

Introduction: Colonoscopy is the preferred modality for colorectal cancer (CRC) screening, follow-up of positive stool-based screening tests, and for polyp surveillance. It is important to monitor the safety of colonoscopy. The study aims to measure the incidence of major complications occurring during outpatient screening colonoscopy at Grady Hospital.

Methods: We retrospectively analyzed data of all asymptomatic patients who underwent outpatient colonoscopy for CRC screening, follow up of a +FOBT, and polyp surveillance between 7/1/2011 and 1/30/2015. Excluding colonoscopies performed for evaluating rectal bleeding, abdominal pain, and other GI symptoms. Patient's demographics, procedure indication, and complications were analyzed. Major complications were defined as any event related to the procedure and requiring admission within 30 days of the procedure (perforations, post polypectomy bleeding, cardiopulmonary and neurologic events).

Results: 9253 colonoscopies were performed during the study period, 6501 procedures were performed on 6152 patients for purposes of CRC screening, polyp surveillance, or FOBT positive stool (all under moderate sedation). Four patients experienced major complications (incidence of 0.6/1000 colonoscopies). One patient had rectosigmoid perforation unrelated to polypectomy, and required primary surgical repair without resection. Two patients had severe post-polypectomy bleeding required admission, blood transfusion, and endoscopic hemostasis. One patient with a known history of seizures had a generalized tonic-clonic seizure after initial sedation prior to scope insertion. No deaths reported.

Conclusion: The incidence of major complications during colonoscopy performed for CRC screening was found to be low (0.6/1000 colonoscopies). This reaffirms the safety of colonoscopy in outpatients undergoing CRC screening.

#52 (morning session)

Association of bacteremia with arteriovenous access failure in hemodialysis patients

Ahmed SM, Plantinga L, Patzer R, Cobb J, McClellan W

Background: Obesity, female sex, diabetes, peripheral vascular disease, and pacemakers are known risk factors for arteriovenous fistula (AVF) and arteriovenous graft (AVG) failure. We examined whether bacteremia in hemodialysis (HD) patients with AVF/AVG represents an additional, independent risk factor for subsequent AVF and AVG failure.

Methods: We conducted a retrospective observational study among 29,571 U.S. patients from the United States Renal Data System who started HD with AVF and AVG between 1/1/2009 and 9/30/2010. We used inpatient ICD-9 codes after dialysis start to define bacteremia and AVF/AVG failure. We then used a multivariable Cox proportional hazards model to assess relationship between exposure to bacteremia and time to access failure.

Results: Overall, 12.2% of patients with bacteremia experienced an access failure, compared to 4.0% of patients without bacteremia ($P < 0.001$). This difference persisted over a median follow-up of 582 days. [Figure 1] With adjustment for known confounders, patients who had bacteremia after dialysis start were at >3-fold greater risk of subsequent access failure, relative to those who did not (HR=3.18, 95% CI: 1.71– 5.95).

Conclusion: This observational study indicates that decreased AVF and AVG survival may be associated with exposure to bacteremia among HD patients.

#46 (afternoon session)

A tissue engineered hybrid myocardial patch for post-MI cardiac regeneration

Andukuri A, Ban KW, Kim S, Jeon YH, Lee SJ, Yoon YS

Applicability of human pluripotent stem (hPSC) cells for cardiac regeneration is limited by poor modes of delivery and impurity of hPSC derived cardiomyocytes (hiPSC-CM) and endothelial cells (hiPSC-EC). There remains an unmet need to deliver purified cells and promote their survival, retention, and engraftment. Therefore, the goal of this study is to develop a tissue engineered hybrid myocardial patch comprising a biomimetic scaffold and a cell mixture of purified hiPSC-CMs, -ECs, and human dermal fibroblasts. The scaffold consists of nitric oxide releasing peptide amphiphiles (PA-YK-NO) with laminin derived cell adhesive ligands and enzyme mediated degradable sites, and electrospun polycaprolactone (ePCL). Overall, we hypothesize that this patch will improve cardiac function through increased cell survival, retention, and functionality. PA-YK-NO, ePCL, and purified populations of PSC-CMs and PSC-ECs were generated as previously described. Cells were seeded on PA-YK-NO and adhesion was analyzed via calcein AM. Viability after encapsulation with PA-YK-NO was analyzed via Live/Dead assay. They were also analyzed for expression of CDH5, ACTN2, and TNNT2. Both cells showed higher adhesion on PA-YK-NO. PSC-CMs and -ECs showed similar viabilities in the

presence and absence of hydrogen peroxide, indicating that PA-YK-NO provided protection against oxidative stresses. After 5 days, PSC-ECs displayed CDH5 expression, and PSC-CMs displayed ACTN2 expression. In addition, in co-culture with HDF, PSC-CMs and PSC-ECs robustly adhered and survived, supporting the feasibility of the approach. Future studies will include the analysis of in vitro functionality of PSC-ECs and PSC-CMs in PA-YK-NO, followed by in vivo analysis in a rat model.

#2 (afternoon session)

Majority of XDR TB cases are due to transmission in a high HIV prevalence setting

Auld S, Shah NS, Brust JCM, Mathema B, Mthiyane T, Ismail N, Moodley P, Mlisana K, Allana S, Smith JP, Gandhi NR

Introduction: The Metabolic Syndrome (MetS) is highly prevalent, afflicting a third of U.S. adults, and confers higher cardiovascular morbidity and mortality. While lifestyle modifications are the first-line of MetS treatment, sustained adherence is achieved by a minority of patients. We investigated the effects of a Health Partner (HP) intervention on MetS.

Methods and Results: 119 university employees with MetS (51±9 years, 59% women) were enrolled in a program that promotes clinical self-knowledge and healthier lifestyles at the Center for Health Discovery and Well Being. Baseline anthropometric, laboratory and vascular function measurements were used by the HP to generate an action plan that included strategies to improve dietary and exercise habits, and subjects were followed up to 2 years. Repeated measures ANOVA showed significant changes in waist circumference ($p=0.007$; baseline vs. 2 years: 103 vs. 98 cm), weight ($p=0.004$; 216±35 vs. 205±37 lbs), body fat percent ($p=0.04$; 39±7 vs. 38±8), fasting insulin levels ($p=0.03$; 11±8 vs. 7.9±10 μ IU/ml), low density lipoprotein ($p=0.005$; 115±31 vs. 105±29 mg/dl), as well as a reduction in carotid-femoral pulse wave velocity ($p=0.02$; 7.4±2 vs. 6.7±1 m/s), systolic ($p=0.001$; 131±18 vs. 126±14 mmHg) and diastolic blood pressure ($p=0.006$; 85±11.1 vs. 80±10).

Conclusion: A personalized, goal directed HP intervention improves abnormalities associated with MetS, including significant blood pressure improvements that accompanied decreased central arterial stiffness. These improvements were sustained after two years of follow-up. Whether HP intervention improves long-term outcomes and whether it is cost-effective needs further investigation.

#6 (morning session)

Sedentary activity in adults with stroke

Bailey RR, Lang CE

Background: Sedentary activity is a risk factor for stroke, independent of physical activity. In order to target sedentary

activity for intervention in this population, patterns of sedentary activity accrual must be understood.

Purpose: To compare sedentary activity between adults with stroke and nondisabled adults.

Methods: Community-dwelling adults with stroke (>6 months, $n=48$) and nondisabled adults ($n=74$) wore accelerometers on their non-paretic (stroke) or dominant (nondisabled adults) wrist for 24.9±0.6 hours during a typical weekday. Actilife 6 software was used to identify sedentary activity. Variables of interest included duration of sedentary activity, number of sedentary bouts, and length of sedentary bouts. A bout was defined as at least 10 minutes of continuous sedentary activity.

Results: Mean duration of sedentary activity was greater in stroke (20.6±1.7 hours) than in nondisabled adults (16.1±2.0 hours, $p<0.001$). Mean number of sedentary bouts was higher in stroke (20.0±5.6) than in nondisabled adults (16.3±4.6, $p<0.001$). There was no difference in length of sedentary bouts between stroke (median (IQR): 20 (19) minutes) and nondisabled adults (median (IQR): 21 (20) minutes, $p=0.10$).

Conclusion: Duration of sedentary activity was high in both groups, but greater in adults with stroke. Adults with stroke experienced a greater number of sedentary bouts compared to nondisabled adults, but bout length did not differ between groups. The number of sedentary bouts and bout length inadequately account for the total duration of sedentary activity in either group, which suggests that sedentary activity is accrued in numerous, short intervals (i.e. <10 minutes) over time.

#5 (morning session)

Controlled comparative outcomes evaluation of endoscopic and surgical management for early Barrett's related esophageal cancer

Barnes JA, Krasinskas AM, Force SD, Clermont MP, Keilin SA, Cai Q, Willingham FF

Objective: For patients with early Barrett's related esophageal cancers, small tumor size, and favorable histologic features, endoscopic therapies are now considered in treatment paradigms. Endoscopic management may be associated with similar oncologic outcomes and lower rates of major complications; however this has not been examined in a controlled manner.

Methods: Patients with high grade dysplasia and early esophageal cancer (T1a, T1b) were reviewed from a 2011-2015 pathology database. The initial query resulted in 296 patients, and 70 patients met inclusion criteria. Demographics, tumor histology, complications, recurrence, and survival were obtained from a review of the medical record.

Results: Of the 70 patients included in the analysis cohort, there were 14 HGD, 37 T1a, and 19 T1b. All patients underwent endoscopic (67.1%) or surgical (32.9%) management. Over an average follow-up of 25.2 months, the number of patients with hospital readmissions was significantly greater for the surgical group (P=0.008). Two deaths occurred over the period of follow-up, one in each group, neither due to esophageal cancer (P=0.6). Significantly less patients in the endoscopic group experienced major complications (6%) versus the surgical group (48%, P=0.000). The rate of minor complications was 15% for endoscopic management and 39% for surgical (P=0.023).

Conclusion: On preliminary evaluation, survival was similar for patients with early esophageal cancer managed with endoscopy or surgery. There was a significantly higher rate of minor complications, major complications, and readmissions in the surgical group; however, longer follow-up may be required to ensure that oncologic outcomes remain equivalent in both groups.

#21 (morning session)

High dietary phosphorus consumption increases inflammatory T cell cytokine production and decreases bone quality in mice

Beck GR Jr, Yu M, Gilbert LC, Ha SW, Li JY, Pacifici R

Secondary hyperparathyroidism has been investigated as a main contributor to senile osteoporosis however the underlying mechanisms remain to be fully elucidated. A potentially significant, yet understudied modulating factor is the high dietary intake of inorganic phosphate (Pi). High Pi intake is characteristic of the US diet with consumption being at least 50% higher than recommended by the FDA/IOM and serum Pi levels increase with age, particularly in women. High dietary Pi intake is known to increase PTH levels and parathyroidectomy abolishes the bone loss induced by high Pi intake, proving the relevance of PTH in the high Pi intake-induced bone loss. Further, we have determined that T cells play a role in the effects of continuous PTH (cPTH) on bone and that cPTH fails to induce bone loss in mice lacking T cells. We therefore hypothesized that a diet high in Pi increases PTH thereby altering immune system function, creating a low-grade inflammatory state and ultimately negatively impacting bone. To test this hypothesis mice were fed diets with varying Pi content; high (1.8%), normal (0.6%) or low (0.2%) and calcium held constant (0.6%), achievable in the human diet. Mice were analyzed for structural bone indices, serum markers of bone metabolism, and endocrine factors as well as T cell populations and inflammatory cytokine production. A significant increase in inflammatory cytokine production from bone marrow T cells of mice on the HPD was identified as well as an increase in Th17 cells which correlated with a significant decrease in bone structural indices.

#47 (morning session)

PPAR γ enhances clearance of *P. aeruginosa* by inducing Paraoxonase-2, thus inhibiting quorum sensing molecules

Bedi B, Yuan Z, Joo M, Zughaler SM, Goldberg JB, Hart CM, Sadikot RT

The pathogenic profile of *P. aeruginosa* is related to its ability to secrete a variety of virulence factors and promote biofilm formation. Quorum sensing (QS) is a mechanism wherein small diffusible molecules, specifically acyl homo serine lactone, are produced to facilitate communication thereby regulating virulence and biofilm formation. We have previously demonstrated that lipid mediators such as PGD₂ and 15d-PGJ₂ are potent immunostimulators and play a pivotal role in host response to virulent *P. aeruginosa*. However the mechanisms by which these mediators enhance the immune effects are not fully defined. Here we show that enhanced bacterial clearance of *P. aeruginosa* (PAO1) by PGJ₂ is dependent on PPAR gamma activation. Macrophages treated with PPAR gamma agonist (pioglitazone 10 μ mol) showed an enhanced phagocytosis and bacterial killing. We sought to investigate the mechanisms by which PPAR gamma contributes to immune stimulation. Paraoxonase-2 (PON-2) is a member of family of enzymes which has a significant ability to catalyze QS molecules of *P. aeruginosa*. We found that the human PON-2 gene has three binding sites for PPAR gamma within its proximal promoter region. We therefore hypothesized that expression of PON-2 may be regulated by PPAR gamma. To investigate the role of PPAR gamma in the expression of PON-2 we treated macrophages with adeno PPAR gamma (PFU of 10) or siPPAR gamma. We found that expression of PON-2 gene was significantly increased in macrophages and epithelial cells that were treated with AdPPAR γ whereas the expression of PON-2 was attenuated in cells transfected with siPPAR gamma. Cells treated with virulent PAO1(MOI 1 or 10) showed an attenuated expression of PON-2 and PPAR gamma whereas cells treated with mutant PAO1 that lack QS molecules were able to induce PON-2 and PPAR gamma. Together these data demonstrate that virulent *P. aeruginosa* strains which secrete QS molecules may impair the ability of the host cells to mount an immune response by inhibiting PPAR gamma. Our studies suggest a role for PPAR γ immunotherapy for virulent *P. aeruginosa* infections.

#36 (morning session)

Understanding the role of the secreted serine protease, Rv2223c, of *Mycobacterium tuberculosis*

Bizzell EB, Georgieva MG, Rengarajan J

Mycobacterium tuberculosis (Mtb) has evolved multiple strategies to evade host immune defenses and replicate within immune cells. These include alteration of its complex cell wall during intracellular growth, and secretion of effectors that modulate immune responses and enhance pathogen survival. Several pathogenic bacteria use extracellularly secreted

proteases to regulate processes ranging from repression of cytokine production to degradation of surface-associated host proteins. While Mtb encodes several putative secreted proteases, their functions are poorly understood. We have been interested in characterizing the predicted Mtb protease, Rv2223c. Rv2223c is transcribed from a predicted operon with a cell-wall associated serine protease, Hip1 (Rv2224c), with which it shares 52% amino acid identity. Hip1 is involved in modification of the Mtb cell wall during infection, and functions by dampening normal immune responses to Mtb infection. Using the model system *Mycobacterium smegmatis* expressing Mtb Rv2223c, we found that Rv2223c is secreted from mycobacterial cells in a signal-sequence dependent manner and undergoes further autoproteolytic cleavage upon secretion. Additionally, we have observed that Rv2223c interacts with the Hip1 physiological substrate, GroEL2, suggesting potentially overlapping or cooperative functions of these proteases. We hypothesize that Rv2223c is a secreted protease that functions by cleaving Mtb substrates and/or host cell substrates to modify the host response during Mtb infection. Biochemical analyses of Rv2223c to determine enzymatic activity, as well as studies exploring the effects of Rv2223c on Mtb infection of host cells are currently being conducted. These studies will provide insights into the molecular functions of Rv2223c in Mtb pathogenesis.

#22 (morning session)

B cell subsets are epigenetically and transcriptionally dysregulated in systemic lupus erythematosus

Blalock E, Scharer CD, Barwick BG, Jenks SA, Neary BE, Boss JM, Sanz I

Systemic lupus erythematosus (SLE) is characterized by multiple B cell abnormalities, including the production of autoantibodies, a major contributing factor to disease pathogenesis. Epigenetic modifications that drive the early molecular events leading to the activation of autoreactive B cells in SLE remain unclear. We investigated the epigenetic and transcriptional signatures of SLE B cell subsets including activated naive (aN), resting naive (rN), late transitional (T3), switched memory (SM), and double negative (DN) B cells. The methylome and transcriptome of B cell subsets from SLE and healthy control (HC) African American females were simultaneously profiled utilizing reduced representation bisulfite sequencing (RRBS) and RNA-seq, respectively. Chromatin accessibility was determined using assay for transposase-accessible chromatin (ATAC)-seq. Global DNA methylation analysis of total B cells identified 2,686 SLE disease-specific differentially methylated loci surrounding 951 genes. Demethylated genes in SLE B cells included IFN-response genes and negative regulators of the viral response. SLE and HC aN B cells gained DNA methylation at 2,952 loci and lost DNA methylation at 82,313 loci when compared compared to rN B cells, indicating a loss of DNA methylation during the transition from rN to aN B cells. Transcriptome analysis of total B cells identified 334 differentially regulated genes in SLE patients. Individual B cell-type transcriptomes

diverged from one another as cells differentiated from rN to DN B cells. Our results indicate that SLE B cells are epigenetically and transcriptionally distinct from HC B cells, suggesting that SLE B cells may be pathogenically programmed at an early stage of maturation.

#17 (morning session)

An evaluation of proton pump inhibitor continuous infusion use in upper gastrointestinal bleed

Brown JM, Woolard S, Shea L, Jafarimehr E, Dacha S, Keilin S, Christie J

Introduction: Proton pump inhibitor (PPI) continuous infusion (CI) is recommended to for patients with upper gastrointestinal bleeding (UGIB). PPI CI may over-used. We defined usage patterns of PPI CI at two hospitals in the context of clinical guidelines.

Methods: Retrospective analysis on patients receiving PPI CI from July 2014 to March 2015 at the Atlanta VA and Emory Hospital. Main outcome: determining whether the PPI CIs were used in accordance with relevant society guidelines. Secondary outcomes: defining groups that ordered inappropriate PPI CI, determining whether Gastroenterology (GI) consultants were involved in the use of PPI CI, and describing the pattern of GI consultant adherence to society guidelines. Four gastroenterology fellows and one VA Quality Fellow reviewed guidelines, analyzing patient charts to determine whether PPI CI use was appropriate.

Results: 293 patients received PPI CI, and 55.6% of these patients received PPI CI that was inappropriate. Of the 163 inappropriately used PPI CI, Medical Intensive Care Unit teams ordered 60; Medicine Floor teams, 54; Emergency Room providers, 23; GI consultants, 11; Surgery Intensive Care Unit teams, 5. A GI consult was obtained in 144 of 163 cases of inappropriate use; a GI consultant recommended 30.1% of inappropriate PPI CI ordered. 46.6% of patients receiving inappropriate PPI CI did not undergo endoscopy during their hospitalization.

Conclusion: PPI CI is over-used, but with reeducation and administrative controls, overuse may be cut down, benefiting patients and healthcare systems alike.

#27 (morning session)

Binding of a novel IgG3 VH4-34 monoclonal antibody to ssRNA in SLE

Chida AS, Cashman K, Jenks SA, Hartson L, Wang Y, Li QZ, Mohan C, Sanz I

IgG antibodies expressing the idiotope for the 9G4 idiotope, the framework-1 hydrophobic patch (HP) of VH4-34, are expanded in SLE. In particular the antibodies to single stranded RNA (ssRNA) have been implicated in viral infections in SLE. Here, we sought to understand the contribution of VH4-34 antibodies that bind to ssRNA in the pathogenesis of SLE. A panel of 9G4

+ monoclonal antibodies (mabs) was generated from IgD+ CD27- naïve B cells and IgD-CD27+ memory B cells of SLE patients. A total of 30 mabs, were tested for anti-ssRNA binding by ELISA. Two representative antibodies with strong ssRNA reactivity were also tested against a proteome antigen microarray and by immunofluorescence. Out of the 30 mabs with diverse antigenic binding patterns, 2 derived from SLE memory B cells (22%) had strong auto-reactivity with ssRNA. These antibodies also bound other Ags including: apoptotic and B cell binding, dsDNA, chromatin, Ribosomal P, and were also positive for ssRNA. These two antibodies were of the IgG3 subclass and were clonally related. Further, the corresponding 9G4- HP mutant of these two abs showed binding to ssRNA albeit with decreased intensity. Our preliminary results suggest that the anti-RNA response may be abundant in SLE memory B cells and mediated by expanded clones with a predominance of IgG3 antibodies. Larger studies will be required to understand the structural basis, generation and selection of ssRNA antibodies in SLE. Such studies will shed light into the role of exogenous and endogenous RNA antibodies to SLE autoreactivity.

#41 (morning session)

A PmrB-regulated deacetylase required for lipid A modification and polymyxin resistance in acinetobacter baumannii

Chin CY, Gregge KA, Napier BA, Ernst RK, Weiss DS

Emerging resistance to "last-resort" polymyxin antibiotics in Gram-negative bacteria is a significant threat to public health. We identified the *Acinetobacter baumannii* NaxD deacetylase as a critical mediator of lipid A modification resulting in polymyxin resistance, and demonstrated that naxD is regulated by the sensor kinase PmrB. This represents the first description of a specific PmrB-regulated gene contributing to polymyxin resistance in *A. baumannii*, and highlights NaxD as a putative drug target to reverse polymyxin resistance.

#12 (morning session)

Does race play a role in medication adherence in inflammatory bowel disease patients?

Clermont MP, Mandalia, AB, Gardner D, Farraye FA, Iskandar H

High quality care in inflammatory bowel disease (IBD) includes complex medical therapies that require adherence to treatment plans and frequent monitoring. Prior investigations of race and medication adherence in IBD have relied on survey tools and self-reporting. Our aim was to compare medication adherence between African American (AA) and Caucasian (C) IBD patients using objective pharmacy refill data. Methods: After Emory IRB approval, we retrospectively reviewed the charts of IBD patients treated in a tertiary center's IBD clinic between 10/2013 and 03/2014. Medication adherence was determined using electronic pharmacy refill data for the 6 months following a visit to the IBD clinic. Statistical analysis included Mann-Whitney U, Chi-square testing, and a logistic regression analysis. Results: Two hundred

and thirty-seven IBD patient charts were reviewed (53% F, mean age 47); 21.9% AA, 70.9% C, 7.2% other races (33% UC, 65% CD, 2% indeterminate colitis). Among AA patients, 84.6% were adherent to medications (n=44/52), as compared to 88.3% of C patients (n=148/168). This was not statistically significant (p=0.3). In a logistic regression model adjusting for sex, race, prior surgery, and prior hospital admission, younger age was the only significant predictor of poor adherence to IBD therapies (OR= 0.9, 95% CI 0.9-0.98, p<0.01). Conclusions: Evaluation of medication refills in AA and C IBD patients seen in the same clinic revealed no significant differences in medication adherence. The only significant predictor of poor adherence was younger age. This suggests that race-based disparities in medication adherence are decreased with similar access to care.

#55 (afternoon session)

Presenting with AIDS at diagnosis is associated with 24-month viral suppression in patients newly diagnosed with HIV during hospitalization at an urban hospital center

Colasanti J, Goswami ND, Khoubian JJ, Pennisi E, Armstrong W, del Rio C

Background: Little is known about outcomes of patients newly diagnosed with HIV in the hospital. We aimed to characterize patient-level and system-level factors associated with long-term viral suppression (VS) following an inpatient HIV diagnosis.

Methods: Retrospective cohort study in patients newly diagnosed during hospitalization at Grady Memorial Hospital from January 2011 - December 2012. Data were abstracted from medical records and matched with Georgia HIV surveillance data for 24 months after diagnosis. Primary outcome was 24-month VS. Variables with significance by univariate analyses and epidemiologically significant factors were included in a multivariate logistic regression analysis.

Results: 94 patients were newly diagnosed during the study period. Median age was 43 (IQR 30, 51), 77% men, 72% non-Hispanic Black, 77% uninsured, 18% homeless, and 14% crack/cocaine users. At diagnosis the median CD4 was 83 cells/ μ L (IQR 18, 264) and 66% had AIDS (CD4 < 200 cell/ μ L or presence of an OI). 68% linked to care within 90 days of hospital discharge. 38% of patients achieved 24-month VS. In univariate analyses, AIDS and being born outside of the United States were associated with 24-month VS. In a multivariate analysis having AIDS (OR 6.053, 95% CI 1.77-20.70) was associated with 24-month VS.

Conclusion: Most patients with new diagnoses during hospitalization still present with advanced HIV. AIDS at diagnosis was most strongly associated with achieving long-term VS after inpatient diagnosis.

#16 (afternoon session)

Treatment of severe aortic stenosis in patients with end-stage renal disease on dialysis

Condado JF, Maini A, Thourani V, Devireddy C, Leshnowar B, Mavromatis K, Sarin EL, Stewart J, Guyton R, Simone A, Keegan P, Block PC, Babaliaros V

Background: Though transcatheter or surgical aortic valve replacement (TAVR or SAVR) are the accepted treatment for severe aortic stenosis (AS), it is unclear whether these therapies are beneficial in patients with concomitant end-stage renal disease (ESRD) on dialysis. Balloon aortic valvuloplasty can be used as palliative therapy in patients with poor life expectancy. A comparison between the three treatment strategies has never been done.

Methods: We retrospectively reviewed patients with ESRD on dialysis that underwent treatment for severe symptomatic AS between July 2007 and June 2015. Patients were classified according to the ultimate treatment received into BAV only, TAVR or SAVR group. Baseline characteristics and 30-day procedural outcomes were compared between the groups. A survival analysis was performed to determine the 1-year survival after each therapy adjusting for STS PROM score.

Results: 89 patients with severe AS and ESRD on dialysis were treated at our institutions: 25 patients with BAV only, 32 with TAVR and 31 with SAVR. Patients in the SAVR group were younger (63 vs. 71 years, $p=0.001$), had less severe COPD (9.7% vs. 28% vs. 25%, $p=0.05$) and prior cerebrovascular disease (3.2% vs. 12% vs. 31.3%, $p=0.008$) than BAV and TAVR patients. There was also a statistical trend to lower STS scores in the SAVR group (9.4% vs. 13.5% vs. 13.5%, $p=0.07$). Though no significant difference in 30-day survival, BAV treated patients had a marked decreased 1-year survival when compared to those treated with TAVR or SAVR (BAV=87.0%, TAVR=40.9%, SAVR=40.0%, $p=0.001$), even after adjusting for STS score.

Conclusions: Patients with severe AS and concomitant ESRD should be treated with TAVR or SAVR. Further studies are needed to compare these two strategies in larger cohort of patients.

#26 (morning session)

Human IgE plasma cells in bone marrow long lived plasma cell subset

Corrado A, Kyu S, Tipton CM, Wise S, Lodi U, Chiang KY, Waller E, Lee FE

IgE serum titers are often high in asthmatic/allergic patients, even in the absence of stimuli, implying that IgE-secreting plasma cells might be maintained over time. The aim of this study is to investigate whether high IgE serum levels are sustained by the ongoing generation of short-lived plasma cells (SLPC) or if a subset of long-lived plasma cells (LLPC) exists in specific survival niches and acts as a memory compartment and a continuous source of IgE antibodies. We found that the

frequency of IgE Antibody-Secreting-Cells (ASC) is higher in allergic or asthmatic patients compared to healthy donors and increases during the allergy season. No differences were seen in the frequency of ASC subsets between healthy donors and high IgE subject in the steady state, while during the allergy season, the frequency of circulating SLPC and LLPC increased. We studied the cellular source of human IgE in both SLPC and LLPC compartments of the blood, nasal-polyp (NP), and bone marrow (BM). IgE ASC frequencies are higher in NP than in any other tissue, and the majority of IgE transcripts were present in pop 2 of SLPC (CD19+CD38hiCD138-). In the BM, IgE-transcripts were found not only in both SLPC subsets (pop A: CD19+CD38hiCD138- & pop B: CD19+CD38hiCD138+) but also in the LLPC subset (pop D: CD19-CD38hiCD138+). We demonstrate that the cellular origin of human IgE plasma cells is the short-lived ASC subsets in NP, but in the BM, IgE plasma cells can be found in both short-lived and long-lived plasma cells.

#2 (morning session)

Predictors of lymph node metastases with resectable pancreatic cancer

Dacha S, Kim S, Gamboa A, Keilin S, Cai Q, Willingham F

Background: In patients with pancreatic adenocarcinoma, the number of lymph nodes involved have been proposed as significant predictors of survival. However, the clinico-pathological predictors of nodal metastases with resectable pancreatic adenocarcinoma have not been systematically evaluated.

Methods: Data from the Surveillance Epidemiology and End Results (SEER) database was abstracted from 2004 to 2010 for patients with resectable pancreatic adenocarcinoma. Univariate and multivariate analyses were performed to evaluate for predictors of nodal metastases with resectable pancreatic adenocarcinoma.

RESULTS: There were 42,747 patients with pancreatic cancer in the initial dataset. Patients with resectable pancreatic adenocarcinoma (4,043 patients) were included in analysis cohort. Of the 4,043 patients, 3,204 patients had confirmed pathologic evaluation of lymph nodes, and were included in the analysis. Of these, 2,110 (65.9%) patients had at least one positive lymph node, and 1,094 (34.1%) had negative lymph nodes. On univariate analysis, the primary site (p -value < .001), grade (p -value < .001), T-stage (p -value < .001), age (p -value < .010), and tumor size (p -value < .001) were all significantly related to nodal metastasis. On multivariate analysis, primary site (p -value < 0.001), grade (p -value < 0.001), T-stage (p -value < 0.001), age (p -value < 0.001), and tumor size (p -value .001) were all significantly related to nodal metastasis.

Conclusion: Lymph node metastasis was more common with tumors in the head of pancreas, with larger tumors and with higher T-stage lesions. An understanding of the rates and predictors of lymph nodal metastasis in potentially resectable

pancreatic adenocarcinoma could inform clinical decision making regarding pre-operative biopsy and neo-adjuvant chemotherapy.

#54 (afternoon session)

Outcomes and quality of life assessment after per oral endoscopic myotomy (POEM): Emory experience

Dacha S, Phillips G, Keilin S, Willingham F, Cai Q

Introduction: Per oral endoscopic myotomy (POEM) has emerged as a promising option for treatment of achalasia. The purpose of this study is to assess outcomes and improvement in quality of life metrics after POEM at a major tertiary referral center.

Methods: We performed a retrospective review of data for patients who underwent POEM. A short form 36(SF36) obtained by either direct interview or telephone interview for pre procedure, 1 month, 3 months, 6 months and 1 year after POEM procedure were analyzed. Normally distributed data were analyzed using a paired t test. SF-36 was expressed as medians and analyzed using the Wilcoxon signed-rank test.

Results: Overall, patients who underwent POEM for achalasia had a significant improvement in dysphagia. Mean Eckardt score was 9.38 \pm 1.53 prior to POEM and 2.65 \pm 1.22 after the POEM (P = 0.001). Pre procedure and post procedure mean LES pressure was 28.52 \pm 11.43 mmHg and 12.15 \pm 4.54 mm Hg respectively. (P = 0.001). SF-36 questionnaires demonstrated a significant improvement in several domains. At 1 month (n=30) all domains other than physical functioning and role limitation due to physical functioning domains were significantly higher. At 3 months (n=29) and 6 months (n=23), all domains other than physical functioning were significantly higher. At 1 year (n=9), bodily pain, vitality, social functioning and mental health were significantly higher.

Conclusion: This Study demonstrates excellent outcomes after POEM for achalasia with significant relief of symptoms, reduced pressure at esophageal manometry and significant improvement in several domains of quality of improvement. Postoperative GERD with PPI use was seen in 8/30 patients.

#46 (morning session)

Neisseria gonorrhoeae antimicrobial susceptibility among men by HIV status, Gonococcal Isolate Surveillance Project (GISP), 2010–June 2014

Kirkcaldy RD, Soge OO, del Rio C, Kubin G, Riedel S, Papp JR, Hook EW III

Background: N. gonorrhoeae (NG) antimicrobial resistance in the US varies by gender of sex partner with infections in men who have sex with men (MSM) exhibiting greater prevalence of resistance than infections in men who have sex exclusively with

women (MSW). Little is known, however, about whether NG resistance differs by HIV status.

Methods: GISP conducts surveillance of antimicrobial susceptibility among urethral isolates from men attending U.S. STD clinics. HIV status at the time of the clinic visit is based on patient report or documentation of a positive test. Antimicrobial susceptibility is determined by agar dilution. Proportions of isolates with resistance or reduced susceptibility were compared by chi-square or Fisher's exact test.

Results: 25,249 isolates were collected during 2010–June 2014; 21,483 (85.1%) had gender of sex partner and HIV data. Of those men, 33.1% (n=7,103) were MSM. MSM were more likely to be HIV-infected (25.3%) than MSW (1.5%, p<0.001). Isolates from MSM had greater prevalence of resistance or reduced susceptibility than isolates from MSW. Among MSM, no significant differences in resistance or reduced susceptibility were observed by HIV status except for reduced azithromycin susceptibility (which was more common in HIV-uninfected MSM). Among 14,380 MSW, however, the prevalence of resistance or reduced susceptibility was higher among isolates from HIV-infected than uninfected men.

Conclusions: Prevalence of NG resistance is high among HIV-infected and uninfected MSM. In HIV-infected MSW, the prevalence of NG resistance also appears high; misclassification of gender of sex partner is possible and might influence these findings.

#30 (afternoon session)

AMPK activation increases urine concentrating ability in a rat model of congenital nephrogenic diabetes insipidus

Efe O, Ren H, LaRocque L, Klein JD and Sands JM

Background: The urine concentration mechanism is regulated by vasopressin which activates NKCC2, urea transporters (UT-A1) and aquaporins (AQP2). Congenital nephrogenic diabetes insipidus (NDI) is caused by vasopressin receptor (V2R) mutations. We studied AMPK as a candidate to stimulate transporters involved in urine concentration in NDI.

Methods: Tolvaptan (10 mg/kg/day), a selective V2R antagonist, was given orally to rats for 4 days, +/- metformin (800 mg/kg/day). Urine samples were collected daily. Kidneys were dissected into inner medullary (IM) tip, base and outer medulla, and UT-A1, AQP2, and NKCC2 were analyzed by Western blot. Immunohistology was used to localize AQP2, pAQP2, pAMPK, and NKCC2.

Results: Tolvaptan was used to produce a rat model of NDI. Metformin was used to stimulate AMPK as a candidate NDI treatment. Urine osmolality in control rats (mean: 2107 mOsm) was significantly decreased by tolvaptan (mean: 1303 mOsm, p<0.05) and restored to control levels by metformin (mean: 2335 mOsm, p<0.05). Metformin increased protein abundance of IM tip UT-A1 (61%, p<0.05) and AQP2(44%, p=0.057) in tolvaptan treated rats. In contrast, IM base UT-A1 and AQP2 levels were not changed with AMPK stimulation. Outer medullary NKCC2

abundance was increased 117% with AMPK stimulation in control rats ($p=0.004$) but not in V2R-blocked rats. Immunohistochemistry showed that AQP2 and p-AQP2-Ser256 membrane localization was increased with acute and chronic AMPK stimulation.

Conclusion: These results indicate that specific AMPK pathway activators might provide a promising treatment for congenital NDI by activating UT-A1 and AQP2.

#13 (morning session)

Levels of assistance concordance and discordance: implications for acute care physical therapy referrals

Elkins JS, Sanford JA, Harrell AJ, Griffiths PC

Background: Hospital stays have shortened since PPS in 1984, down from 10.7 days on average to 5.7 in the over 65 age group. Hospitals have adopted business strategies and management techniques aimed at improving quality of care but, moreover, to reduce costs especially personnel costs. Increasingly even by their own organization, the APTA, acute care hospital based physical and occupational therapy services have been called into question for both their evidence base and their financial contributions. Recently a few studies have focused on "complex skills" in the ICU; however, almost no evidence exists about the value of physical and occupation therapy on the medical/surgical floor in hospitals.

Methods: This study uses data from the CG Skills study, a study conducted by the VA and focused on caregiver dyads. The caregiver answered questions and rated the care recipient's level of assistance required for bathing, dressing, transferring, and toileting. For the intervention group, a clinical expert, a physical or occupational therapist, evaluated the levels of assistance required by the care recipient.

Results: Discordance exists between the caregiver rating of levels of assistance and the clinical expert. Even when the level of assistance as rated by the caregiver was 0% the rating by the clinical expert did not agree. The area of most discordance was bathing.

Discussion: The level of discordance in assistance levels in functional activities indicates patients should be assessed by a clinical expert during the acute hospital stay prior to discharge to ensure adequate discharge planning.

#4 (afternoon session)

Person environment fit theory - assisted living facilities

Elkins JS, Hawes C

Background: Powell Lawton pioneered extensive work in environmental press in assisted living facilities (ALFs) beginning in the 1980's. His work focused on achieving a balance in the "press" of the environment so that residents would neither feel too stressed nor too bored. Person-environment fit theory was conceptualized when the population rate of dementia in ALFs was 25%. Most facilities still embrace Lawton's original model.

While the 2010 National Survey of Residential Care Facilities (NSRCF) does reflect a newer population-based percentage of just over 40% it is commonly thought by many researchers and clinicians that the number of people living in assisted living with dementia is significantly higher – sometimes approximating 100% of residents. To better serve the residents of today facilities may need to have different services and supports.

Method: Using the 2010 NSRCF we conducted a second order confirmatory factor analysis to re-examine the Lawton model and to conceptualize a new model for assisted living facilities.

Results: Using constructs from Lawton's model the confirmatory factor analysis yields results leading us into an exploratory factor analysis to reveal the common factors present. This model using exploratory then confirmatory factor analysis yielded a model with specific health services and supports.

Discussion: For contemporary residents a model of assisted living reflecting the need for increased services such as incontinence services and increased medical support offers an alternative or update to the original Lawton model where having a parking space remains as a construct.

#9 (afternoon session)

Comparison of outcomes between individuals with pure and mixed lupus nephritis: a retrospective study

Enofe N, Fevrier HB, Ilori TO, Oommen A, Cobb J, Navarrete J, Adedinsewo D, Osikoya O, Farris AB, Plantinga L

Lupus nephritis (LN) is divided into six classes (ISN/RPS Class I to VI) but can occur as a mixture of two classes. Pure proliferative LN (PPLN) comprises Class III or Class IV only, while mixed proliferative and membranous LN (MPLN) comprises combinations of Class III & V or Class IV & V. We compared individuals with biopsy-proven PPLN vs. MPLN in terms of clinical presentation, outcomes of complete and partial remission or End Stage Renal Disease (ESRD), and clinical predictors of outcomes. LN patients were identified from a native renal biopsy registry containing biopsies occurring between January 2000 and December 2011 (PPLN $n=60$ and MPLN $n=96$). The association between LN category and time to remission ($\geq 25\%$ improvement in estimated Glomerular Filtration Rate (eGFR) if baseline was abnormal and the urine protein creatinine ratio was less than 0.5) or progression to ESRD was assessed using multivariable Cox proportional hazards analysis. The population was predominantly female (84.0%) and African American (71.8%), with a mean age of 33.4 years. The median follow-up time was 1.5 years. Using the PPLN group as the reference group, no association was found between MPLN and time to remission (HR=0.13, 95% CI=0.01-1.36) or ESRD (HR=0.30, 95% CI=0.07-1.26). While baseline eGFR was significantly associated with time to remission (HR=0.90, 95% CI=0.84-0.98), no significant differences in remission or development of ESRD between patients with PPLN or MPLN was found. However, we demonstrated that higher baseline eGFR is an important factor in achieving remission in individuals with LN.

#22 (afternoon session)

HIV-1 decreases Nrf2/ARE activity and phagocytic function in alveolar macrophages

Fan X, Staitieh BS, Neveu W, Ding L, Raynor R, Spearman P, Guidot DM

Respiratory complications are a frequent complication in HIV-infected individuals. HIV-related oxidative stress contributes to impairment of alveolar macrophage functions such as phagocytosis and consequently increases the host's susceptibility to pathogens. We hypothesized that Nrf2, a master transcription factor that activates the anti-oxidant response element (ARE) and thereby regulates defenses that protect cells from oxidative stress, plays an important role in alveolar macrophage immune function in HIV-infected individuals. Here, we reported that primary alveolar macrophages (AMs) isolated from HIV Tg rats had significantly decreased expression of Nrf2 and the downstream Nrf2-dependent genes NQO1 and GCLC compared to AMs from Wt rats. Treating NR8383 cells (rat macrophage cell line) with HIV-1-related protein gp120 or Tat similarly decreased the gene (and protein) expression of Nrf2, NQO1 and GCLC. Further, HIV infection of human monocyte-derived macrophages likewise inhibited gene and protein expression of Nrf2, NQO1 and GCLC. In both primary cells and macrophage cell line, phagocytosis as reflected by phagocytosis of fluorescent bacteria was decrease when cells exposed to HIV-1-related proteins. Importantly, treating AMs from HIV Tg rats with sulforaphane (a Nrf2 activator) significantly improved their phagocytic function. Our findings demonstrate that HIV-1 infection, likely via exposure to HIV-1-related protein, inhibits Nrf2 expression and its ability to activate ARE-dependent genes in alveolar macrophages and in parallel (or as a consequence) impairs phagocytic function. We speculate that treatments targeted at increasing Nrf2 activity could enhance lung innate immunity in person living with HIV-1.

#8 (afternoon session)

Conformity to the Mediterranean diet and renal outcomes in patients with chronic kidney disease from the chronic renal insufficiency cohort

Fevrier HB, Ilori TO, Wang X, Enofe N

In the United States there are a growing number of individuals who suffer from chronic kidney disease. An improved and balanced diet is recommended for individuals with chronic kidney disease, and may slow the progression of the disease which can result in end stage renal disease. A Mediterranean diet has been previously associated with decrease risk of death and cardiovascular disease. A sample of 3,231 patients, enrolled in the Chronic Renal Insufficiency Cohort between 2003 and 2008, was assessed using diet history questionnaires given at the baseline visit. A diet score, ranging from 0-10, was calculated for each study participant using 10 food components from the diet history questionnaires, where a higher number indicates higher conformity to a Mediterranean diet. The median diet score was 4. The mean age was 58.3 (SD=11.0) and the median energy intake was 1638.04 (interquartile range: 1,222.5, 2,276.0). Higher conformity to a Mediterranean diet was associated with

decreased risk of death (hazard ratio: 0.892, 95% confidence interval: 0.829, 0.960). In addition, a higher diet score was associated with a decreased risk in end stage renal disease or a 50% decline in estimate glomerular filtration rate. The final model was adjusted for sex, age, race, energy intake, body mass index, income, education, diabetes, hypertension, and pre-existing cardiovascular disease. Conformity to a Mediterranean diet may be associated with a decreased risk of death and with a slower progression of chronic kidney disease.

#16 (morning session)

Development of a clinicopathologic kidney biopsy database using billing and diagnosis codes: a descriptive study

Enofe N, Fevrier HB, Ilori TO, Adedinsewo D, Oommen A, Cobb J, Navarrete J, Osikoya O, Rahbari-Oskoui F, Farris AB, Plantinga L

A growing kidney disease population coupled with expanded use of electronic medical records presents a unique opportunity for regional translational clinical research. In collaboration with clinicians, pathologist and data informatics, we developed a comprehensive registry of all native renal biopsies at a major hospital in the Southeastern US and described the pattern of glomerular diseases using clinicopathologic diagnosis. We identified all native percutaneous renal biopsies (n=2,245) performed on adults (>18) between 2000 and 2011 using CPT and ICD-9 billing codes. Transplant biopsies and cytopathology were excluded. Renal pathology reports were reviewed by two independent clinical nephrologists and a clinicopathologic diagnosis was entered for all patients. Clinical, laboratory and demographic data were extracted and validated by an independent chart review. Descriptive and bivariate statistics were used to analyze patient characteristics at biopsy. Patients had a mean age of 44.2 years; approximately half were male and the majority was African American (40.7%). Lupus nephritis (n=278, 12.4%) was the most prevalent renal diagnosis. Among primary glomerular diseases, focal segmental glomerulosclerosis (FSGS) was the most prevalent (136, 9.2%), followed by IgA nephropathy (123, 8.3%), and membranous glomerulonephritis (GN) (69, 4.6%). Diabetic nephropathy was the most common secondary GN (97, 6.5%) followed by ANCA-associated vasculitis (31, 2.1%). Other diagnoses included hypertensive nephropathy, thrombotic microangiopathy, HIV nephropathy, amyloidosis and multiple myeloma which were all less than 2%. We successfully established a kidney biopsy registry at our center, which will be instrumental to studying outcomes in this rare group of diseases.

#40 (morning session)

Protection enhancement of a chimeric multi-stage malaria vaccine with the use of adenoviral vectors in heterologous immunization regimens

Fonseca JA, Cabrera-Mora M, Dmitriev I, Curiel DT, Blackwell J, Moreno A

An effective malaria vaccine is required to reduce the burden of the infection and ultimately control the disease. Given the complexity of the parasite-host interaction, an ideal malaria

vaccine should target several parasite stages inducing anti-parasite and anti-disease immunity. A major challenge for the development of an effective multi-stage vaccine is to induce robust cellular and humoral immune responses. To this day a regimen able to induce such balanced responses is not available. We reported a *P. yoelii* chimeric recombinant protein (PyLPC-RMC) derived from two malaria antigens, linked to cognate promiscuous T cell epitopes. This vaccine had superior efficacy, mediated by CD4+ T cells and neutralizing antibodies, compared to non-chimeric constructs. With the aim of inducing CD8+ T cells, we produced adenovirus (Ad) vectors expressing PyLPC-RMC as a transgene and tested several Ad-Protein prime-boost regimens to improve protective efficacy. The common Ad5 vector platform has low immunogenicity give the high prevalence of human anti-vector neutralizing antibodies. To overcome this limitation, we developed a chimeric Ad5/3 vector where the Ad5 knob region was replaced with the one from the rare Ad3, allowing the vector to circumvent preexisting anti-Ad5 immunity. The immune responses elicited by immunization with Ad5 or Ad5/3 were comparable. Our data highlights that immunization with the Ad5/3 vector induces a protective immune response against *P. yoelii* infection that depends on antibodies, CD4+ and CD8+ T cells. This is the first time that the chimeric Ad5/3 vector has been used for malaria vaccine development with a successful protective response.

#10 (morning session)

Beyond Tuskegee: early results of a community randomized study of a faith-based program to improve clinical trial participation among older Southern African Americans

Frew PM, Schamel JT, O'Connell KA, Randall LA, Boggavarapu S

This study evaluated the effectiveness of an intervention to address the significant underrepresentation problem of clinical trial participation among older Southern African-Americans. We recruited 221 persons ages ≥ 50 years from six predominantly African American churches, randomized to intervention and comparison churches. The intervention included three educational sessions about clinical trials and health disparities; control participants only completed questionnaires during sessions. Both groups received study newsletters and notifications about clinical studies seeking participants. Multivariable linear mixed effects models examined information-seeking and clinical trial intentions, in addition to within-group longitudinal changes. For the intervention group, motivation to obtain clinical trial information increased from baseline to 3-months ($p < 0.05$), and from baseline to 6-months ($p < 0.05$). Additionally, baseline intention to join clinical trials was positively related to 3-month intentions ($p < 0.05$). Age was related to 3-month ($p < 0.01$) and 6-month ($p < 0.01$) intention to seek information. Older participants indicated less intention to join clinical trials at 3-month ($p < 0.0001$) and 6-months ($p < 0.05$). Although the intervention was not significantly associated with outcome measures, a trend towards increased intentions to seek information about and join clinical trials was observed. The results therefore suggest that socioenvironmental factors related to the intervention may have contributed to these outcomes.

#3 (afternoon session)

Understanding multilevel factors contributing to women's entry, engagement, and adherence to HIV treatment and care

Frew PM, Holstad MK, Zuniga J, Braxton ND, Sarkodie EP, Robinett HE, Ofotokun I, Wingood GM

Background/Objectives: Women living with HIV face unique barriers to HIV treatment, affecting their ability to reach HIV continuum of care (CC) outcomes. This qualitative study explored women's HIV care obstacles.

Methods: We conducted purposive sampling and interviews with 34 women who retrospectively experienced challenges at different CC milestones prior to enrollment in the Atlanta Women's Interagency HIV Study (WIHS). We conducted constant comparative analyses linking sociobehavioral and biomedical data to cases that resulted in a three group behavioral typology.

Results: "Care-Engaged" women (N=10) described positive healthcare experience, prompt linkage to care, strong social and healthcare provider relationships, and high CD4 (≥ 800) and suppressed viral load value post-diagnosis. "Care-Inconsistent" women (N=7) described challenges related to housing, unsupportive healthcare institutions, and perceived HIV stigma as barriers to care. Supportive healthcare providers and institutions, social and emotional support, and viral suppression within 6 months of treatment were cited as care facilitators, with healthcare provider insistence as a frequently cited intervention for entering treatment. "Care-Detached" women (N=4) described unstable housing, unsupportive healthcare institutions, and drug and alcohol abuse as challenges to care. Supportive social groups and healthcare providers, community-based programs, support groups and mental health services, and knowledge of HIV and HIV treatment were cited as care facilitators.

Conclusions/Implications: This study identified factors that influence women's HIV treatment and care; however, each group still faces multilevel factors that threaten HIV CC. There is consistency among healthcare experience and strong social support, but inconsistencies among other factors suggest a need for specific subgroup interventions.

#29 (afternoon session)

Polymerase delta-interacting protein 2 regulates collagen accumulation via activation of the Akt/mTOR pathway in vascular smooth muscle cells

Fujii M, Amanso A, Abrahão TB, Lassègue B, Griendling KK

Objectives: Polymerase delta interacting protein 2 (Poldip2) has previously been implicated in migration, proliferation and extracellular matrix (ECM) production in vascular smooth muscle cells. To better understand the role of Poldip2 in ECM regulation, we investigated the mechanism responsible for excess collagen I accumulation in Poldip2 \pm mouse aortic smooth muscle cells (MASMs).

Approach and Results: Protein degradation and protein synthesis pathways were investigated. Depletion of Poldip2 had no effect on proteasome activity, but caused a 40% reduction in autophagy. However, the rate of collagen I degradation was similar in Poldip2^{+/+} and Poldip2^{+/-} MASHs. Conversely, the signaling pathway PI3K/Akt /mTOR, involved in regulation of protein synthesis, was significantly activated in Poldip2^{+/-} MASHs. Suppressing mTOR signaling by Akt inhibitor or Rapamycin prevented the increase in collagen I production, suggesting that Poldip2 may act upstream from PI3K. While collagen I and laminin were increased in Poldip2^{+/-} MASHs, overall protein synthesis was not different from that in Poldip2^{+/-} MASHs, suggesting selectivity for ECM proteins.

Conclusions: Poldip2^{+/-} MASHs exhibit higher activity of the PI3K / Akt / mTOR signaling pathway, leading to increased ECM protein synthesis. These findings have important implications for vascular diseases in which ECM accumulation plays a role.

#33 (morning session)

A case of IgA nephropathy in an HIV-positive patient

Garcia-Sanchez H, Niyyar V, Farris A III, Rogers T

IgA nephropathy has been described in patients infected with HIV. Though IgA levels are commonly elevated in HIV, these patients may also develop IgA antibodies against specific HIV antigens. Renal lesions may result from HIV antigen-specific immune complexes that are derived from the circulation and from in-situ complex formation. We present a case of a patient with HIV/AIDS, on highly active antiretroviral therapy (HAART), who was evaluated for microscopic hematuria and worsening renal function. The patient's only complaint was early morning periorbital edema. On examination, BP was 103/72 mm Hg with a BMI 23 kg/m². Labs showed normal electrolytes, serum creatinine 1.7 mg/dL (baseline 0.7mg/dL), urine protein/creatinine ratio of 2.5 grams/dl. Other serologies were negative. HIV VL was undetectable, and CD4 count was 183. Renal US showed bilateral enlarged, echogenic kidneys. Renal biopsy revealed sclerosing glomerulopathy with IgA immune type deposits on immunofluorescence. The patient was initiated on an ACE inhibitor and a low salt and protein diet, with resolution of his proteinuria to 0.6 Grams/dL. His renal function stabilized, with a creatinine of 1.5 mg/dL. In conclusion, IgA glomerular disease arising in HIV positive patients has clinical and pathologic aspects similar to idiopathic IgA nephropathy. IgA nephropathy should be suspected in patients with HIV presenting with unexplained hematuria, and renal biopsy should be performed as soon as possible for early diagnosis and therapy. Current management recommendations are similar to those with idiopathic IgA, including ACE inhibitors or ARB for control of proteinuria (>1 g / day) or hypertension.

#11 (afternoon session)

Detectable cardiac troponin I predicts adverse cardiac events and heart failure hospitalizations in stable heart failure outpatients

Hammadah M, Georgiopoulou V, Kalogeropoulos A, Butler J, Tang WH

Background: Cardiac troponin I (cTnI) is a sensitive marker of myocardial damage and elevated levels of cTnI have been suggested to predict adverse outcomes in heart failure (HF) patients. However, the prognostic value of cTnI in stable HF outpatients has not been studied before.

Methods: We examined the association between baseline detectable cTnI and clinical events (death, cardiac transplantation or ventricular assist device implantation) and hospitalizations in 175 outpatients with HF enrolled in a prospective cohort study in the metropolitan Atlanta GA area from 1/2008 to 7/2009. Plasma levels of cTnI were measured using the STAT Troponin I assay (Abbott Laboratories, Abbott Park IL) which provides highly sensitive analytical measurement of cTnI with a reported limit of detection reaching 0.001 ng/mL, and a diagnostic cut-off of 0.03 ng/mL for myocardial infarction defined by the upper limit of normal (99th percentile cut-off). Cox regression analysis was used to study association with cardiac outcomes, while negative bi-nominal regression analysis was used to assess risk of HF related hospitalization.

Results: In our population (age 57±12, male 62%, diabetes 34%, coronary artery disease 38%, brain natriuretic peptide 104 (48-274) pg/ml, EF 30±15%), 120 patients had undetectable levels of cTnI (<0.001 ng/ml). Patients with detectable cTnI levels were grouped into those with low normal (cTnI between 0.001 and 0.01, n=17), high normal (cTnI between 0.01 and 0.03, n=18) and high cTnI (≥0.03, n=20). After a mean follow up of 3.5±0.9 years, 34 patients had a clinical event, while 50 patients had at least one HF related hospitalization. Total number of HF related hospitalizations was 167 (range, 0-14). After adjustment for age, gender, diabetes, CAD, ejection fraction, creatinine clearance and log transformed BNP, patients with high normal and high levels of cTnI had significantly increased risk of clinical events [HR (95CI%) of 3.2 (1.2-8.8) and 3.6 (1.5-8.8), (p<0.05 for both), respectively (figure)]. Furthermore, those with high normal and high cTnI had increased incidence rate of HF related hospitalizations in comparison to those with undetectable levels [adjusted incidence rate (95%CI) of 3.0 (1.2-7.7), and 4.1 (1.8-9.3), (p<0.05 for both), respectively].

Conclusion: High normal and high troponin I levels are associated with increased risk of adverse outcomes and hospitalization in stable heart failure outpatients.

#58 (morning session)

High sensitive cardiac troponin T is associated with increased risk of mental stress induced myocardial ischemia

Hammadah M, Al Mheid I, Wilmont K, Ramadan R, Alkhoder A, Awad M, Obideen M, Abdelhadi N, Fang S, Levantsevych O, Bouchi YH, Pimple P, Mohammed K, Murrah N, Raggi P, Shah A, Vaccarino V, Quyyumi A

Background: High sensitive cardiac troponin T (cTnT) is a new marker of myocardial damage and elevated levels of cTnT have been linked to adverse outcomes in coronary artery disease patients. However, the association between cTnT and mental stress induced myocardial ischemia (MSIMI) has not been studied before.

Methods: We evaluated 609 patients with stable CAD using a standardized mental stress test using a public speaking task. 99mTc sestamibi myocardial perfusion imaging was performed. Rest and stress images were visually compared and scored for perfusion abnormalities using a 17-segment model. MSIMI was defined as a new impairment in myocardial perfusion in a segment with a score ≥ 2 or worsening impairment of ≥ 1 above a resting score of ≥ 2 . Cardiac TnT was assessed in plasma before mental stress test using a commercial assay (Abbott).

Results: The average age was 63 ± 9 years, 76% of patients were male, 32% had a history of diabetes and 31% a history of myocardial infarction. Overall, 102 (17%) patients developed MSIMI. Median (IQR) cTnT was 4.3 (2.8-7.3) pg/ml. Patients with MSIMI had significantly higher troponin levels in comparison to those with no ischemia [median (IQR) cTnT of 5.9 (3.9-8.9) vs 4.1 (2.7-6.9), $p < 0.001$]. Furthermore, patients with high cTnT (\geq median; 4.3 pg/ml) were more likely to develop MSIMI (odds ratio 2.7, 95%CI, 1.7-4.3, $p < 0.001$). The association remained significant event after adjustment for demographic factors and traditional CAD risk factors.

Conclusion: Higher levels of cTnT are associated with increased risk of MSIMI.

#11 (morning session)

A pre-intervention qualitative evaluation to inform implementation of a research participation enhancement and advocacy training program for diverse seniors (DREAMS)

Hart AR, Perkins M, Dillard R, Hackney ME

Background: DREAMS is a two-part intervention to address underrepresentation of diverse seniors in clinical research. Part I is an interactive health seminar on aging research presented by clinical investigators; Part II is a research-advocate training course. A pre-intervention qualitative evaluation of older adults' attitudes toward research informs DREAMS curriculum design.

Objectives: To identify potential barriers and facilitators to research participation and inform DREAMS, an educational

intervention designed to engage and actively involve diverse older adults in Patient Centered Outcomes Research (PCOR).

Methods: Four focus groups were conducted with stratified socioeconomic status (SES) groups (low to high), to gauge perceptions and knowledge of clinical research, determine level of prior research participation, identify barriers to research participation, and probe for research topics of interest among older adults. Results: Focus group data from 35 older adults (M age= 74.5 ± 7.4 y; African-American (n=12), Asian (n=1), Hispanic/Latino (n=2), White (n=18), multiracial (n=2)) suggest older adults across socioeconomic strata foster misconceptions about research (e.g., funding, regulation, terminology). For many individuals in the upper-middle (n=10; M education= 17 ± 2.2 y), middle (n=11; M education= 16.5 ± 2.0 y), and lower-middle (n=8; M education= 12.8 ± 2.1 y) SES groups, these negative perceptions likely did not limit their willingness to participate in research whereas most in the lowest SES group (n=6; M education= 10 ± 2.2 y) indicated an unwillingness to participate in research due to distrust of researchers and fear of mistreatment.

Conclusions: This person-centered qualitative pre-intervention evaluation provides important insights that will inform educational and advocacy training programs to be more culturally responsive, attuned to desired audience, and sustainable.

#18 (afternoon session)

Use of CPR-sensing defibrillators to improve outcomes for in-hospital cardiac arrest: a feasibility study

Harzand A, Shah A, Zafari AM

Background: Survival amongst patients who suffer in-hospital cardiac arrest (IHCA) is poor, with reported survival to discharge rates of 6-15 percent. Recent evidence suggests that the use of real-time point-of-care feedback, using CPR-sensing defibrillators, is beneficial in improving cardiopulmonary resuscitation (CPR) quality, however its effect on outcomes for IHCA remains unclear.

Methods: In a single-center retrospective cohort study, we reviewed IHCA event and outcome data between June 2011 and April 2015. Data on CPR-sensing defibrillator (Philips MRx-QCPR) usage was downloaded from defibrillators. Chi square and fisher exact tests were used.

Results: We captured 193 episodes of IHCA for analysis. CPR-sensing defibrillators were only used 4% of the time. ROSC was achieved in 60% of cases. Pulseless electrical activity (PEA) and asystole were the most commonly reported initial rhythm (77%), followed by VF or pulseless VT (14.5%) and undocumented cases (7.8%). There was no difference in rates of ROSC or sustained ROSC > 20 minutes ($p = 0.38$) based on initial rhythm. Survival to discharge and at 1 year was significantly higher in the VF/pulseless VT group than in the PEA/asystole group (46% vs. 14%, $p < 0.0001$, and 30.4% vs. 5.8%, $p = 0.0007$, respectively). Use of CPR-sensing defibrillators was not associated with any improvement in the rates of ROSC in the entire group, regardless of initial rhythm.

Conclusions: CPR-sensing defibrillators for real-time feedback were used only in a small minority of cases and were not associated with any improvement in outcomes. Sustained efforts are needed; larger, better powered studies may better reveal their true effects.

#19 (afternoon session)

Depression is the strongest predictor of angina and is independent of underlying coronary artery disease severity in patients with cardiovascular disease

Hayek SS, Del Mar AS, Awad M, Ghasemzadeh N, Khayata M, Harfouch B, Yadalam A, Shah A, Vaccarino V, Quyyumi AA

Introduction: Angina pectoris (AP) is a hallmark of obstructive coronary artery disease (CAD). Depression is associated with worse morbidity and mortality in patients with CAD. While patients with CAD and depression tend to experience chest pain more frequently than those without depression, it is unclear whether this is due differences in underlying CAD severity.

Methods: 5825 patients underwent left heart catheterization (LHC) between 2004 and 2013 at Emory Healthcare sites and were recruited into the Emory Cardiovascular Biobank. Patients completed the Seattle Angina Questionnaire (SAQ) to assess angina frequency (AF) and the Patient Health Questionnaire-9 (PHQ-9) to screen for depression. A lower AF score is indicative of more frequent chest pain. Higher PHQ-9 scores suggest more depressive symptoms. Angiographic CAD severity was estimated using the Gensini score. Multivariable analysis using linear regression was performed with the AF score as dependent variable and the PHQ-9 and Gensini scores in addition to demographics and clinical characteristics as independent variables.

Results: There was a significant negative correlation between PHQ-9 and AF ($r=-0.284$, $P<0.001$) scores, indicating that angina was more frequent with more severe depression. In a multivariable linear model, both the Gensini, (relative importance 16%, $p<0.0001$), and PHQ-9 (relative importance 69%, $p<0.0001$) scores were independent predictors of AF. PHQ-9 remained an independent predictor of AF even in the subset of patients without significant CAD.

Conclusions: Depression is a major and independent contributor to AP in patients with and without CAD. Whether treatment of underlying depression improves AP needs to be further studied.

#47 (afternoon session)

Lysophosphatidic acid receptor 5 is essential for intestinal stem cell renewal

He P, Zhao L, Neish A, Srinivasan S, Yun CC

The entire intestinal epithelium is replaced every 5 days and the high rate of turnover is fueled by intestinal stem cells (ISCs) localized at the crypt base. Lysophosphatidic acid (LPA), a small lipid molecule, promotes cell proliferation and survival by activation of cognate receptors, LPA1-LPA6. LPA5 is abundantly

expressed in the intestine, but its function is not well understood. In the present work, we aimed to understand the importance of LPA5 for intestinal physiology by using a conditional LPA5 knockout mouse model, *Lpar5^{fl/fl}*. *Lpar5^{fl/fl}* mice were crossed with *Rosa-CreERT2* to generate *Lpar5^{fl/fl};Rosa-CreERT2*, which were treated with tamoxifen (TAM) to delete LPA5. Strikingly, mice with deletion of LPA5 became moribund within 7 days post last TAM injection. The gastrointestinal tract was dilated indicating dysregulation of absorptive functions. Histological analysis showed that intestinal villi were blunted with crypt erosion. Immunohistochemical staining of Ki67 and cleaved caspase 3 revealed decreased epithelial cell proliferation and increased apoptosis, respectively. Of note, crypt cell apoptosis started as early as 2 days after the first tamoxifen administration. The intestinal epithelium has the capacity to repair after chemotherapy or irradiation induced injury. We found that LPA5 deficiency markedly compromised radiation-induced recovery of ISCs. Cultured intestinal crypts form 3-D organoids in matrigel. We showed that acute deletion of LPA5 increased apoptosis and prevented the growth of organoids. Our study reveals a novel function of LPA5 in regulation of survival and maintenance of intestinal stem cells.

#53 (morning session)

Polymerase δ -Interacting Protein 2 regulates astrocyte activation in ischemic stroke

Hernandes MS, Lassègue B, Yepes M, Griendling KK

Polymerase δ -Interacting Protein 2 (Poldip2) is a binding partner of Nox4 NADPH oxidase and carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1). Nox4 and CEACAM1 have been implicated in stroke, but with different outcomes: both contribute to neurodegeneration but only CEACAM1 contributes to blood brain barrier (BBB) dysfunction. However, the underlying mechanisms are still obscure. Our hypothesis is that Poldip2^{+/-} mice may be protected against transient middle cerebral artery occlusion (tMCAO). tMCAO was induced in wild type (WT) and Poldip2^{+/-} mice. The volume of the ischemic lesion was measured in TTC-stained sections. BBB breakdown was evaluated by Evans blue dye extravasation. Poldip2 protein expression was evaluated by immunofluorescence and western blotting. RT-PCR was used to measure mRNA levels of cytokines, MMPs and TIMPs. Astrocytes were transfected with Poldip2 siRNA in culture. Poldip2^{+/-} and WT mice displayed comparable infarct sizes following tMCAO. A decrease in Evans blue dye extravasation was observed in Poldip2^{+/-} mice (25 ± 3 vs $6\pm 2\mu\text{M/g}$). Upregulation of cytokine mRNA following tMCAO was also attenuated in Poldip2^{+/-} mice: MCP-1 (253 ± 34 vs $83\pm 23\text{AU}$), IL-6 (134 ± 38 vs $38\pm 10\text{AU}$), TNF α (39 ± 12 vs $12\pm 3\text{AU}$), MMP-2 (19 ± 3 vs $10\pm 1\text{AU}$), MMP-9 (253 ± 12 vs $13\pm 3\text{AU}$) and TIMP-1 (286 ± 110 vs $61\pm 15\text{AU}$). Poldip2 protein expression increased in the ischemic brain of WT mice (69 ± 4 vs $20\pm 5\text{AU}$) and was predominantly located in astrocytes. Poldip2 protein expression was increased in astrocytes following hypoxia (79 ± 15 vs $27\pm 5\text{AU}$), and Poldip2 siRNA prevented cytokine induction under these conditions. In conclusion, Poldip2 contributes to stroke-induced BBB breakdown via its ability to inhibit a pro-inflammatory response in astrocytes.

#20 (afternoon session)

Early serial SOFA evaluation is independently associated with mortality in patients admitted to the ICU with sepsis

Holder AL, Murphy DJ, Overton E, Lyu P, Martin GS, Buchman TG

Background: The sequential organ failure assessment (SOFA) score is a validated tool associated with mortality in patients with sepsis. The aim of this study is to determine if the incremental addition of serial scores will independently improve prognostication with SOFA.

Methods: This is a retrospective cohort study of patients admitted to 3 hospitals in the Emory Healthcare system from January 2014 to December 2014. Patients aged 18 years or older were included if they met all of the following criteria within 24 hours of hospital admission: (1) 2 SIRS criteria within 4 hours of each other; (2) a positive blood culture; and (3) admitted to the ICU for at least 3 consecutive days. A multivariate model was constructed which included ICU day 1 SOFA score. SOFA scores from ICU days 3, 5, and 7 were incrementally added to that model to identify statistically significant improvement in the area under the receiver operator characteristic (AUROC) curve.

Results: Of the 1414 patients included, 158 (12.6%) died. ICU day 3 SOFA score improved mortality prediction of a model using the score from day 1 (n=1414; AUROC 0.74 vs 0.69; p<0.01). ICU day 5 SOFA score did not improve mortality prediction of a model using scores from days 1 and 3 (n=848; AUROC 0.70 vs 0.68; p=0.21). ICU day 7 SOFA score improved mortality prediction of a model using scores from days 1, 3 and 5 (n=596; AUROC 0.75 vs 0.65; p<0.01).

Conclusions: Serial SOFA assessment improves mortality prediction in septic ICU patients.

#25 (morning session)

A novel population of CD27-IgD- B cells is highly expanded in the bone marrow of systemic lupus erythematosus patients

Hom J, Tipton CM, Fucile C, Wei C, Rosenberg A, Sanz I

Systemic lupus erythematosus (SLE) is a disease where autoreactive antibodies are produced as a result of abnormal B cell activation and broken self-tolerance. In this study, we analyze the bone marrow B cell repertoire of human subjects in order to better understand these defects. Multi-color flow cytometry was combined with deep sequencing of the immunoglobulin heavy chain to distinguish various B cell sub-populations and their effects on the circulating antibody pool. We were able to identify multiple populations of cells that were drastically altered in SLE bone marrow, including a population of activated naive cells whose peripheral counterpart was recently identified and characterized by our lab, and a population of CD27-IgD- cells that were highly clonally-connected to antibody secreting cells (ASC) in the bone marrow and circulation. Strikingly, this population of CD27-IgD- cells displayed much higher levels of somatic mutation than its peripheral counterpart

indicating highly distinct populations of cells. Perhaps most interestingly though, longitudinal analysis showed that ASC clones can persist for at least a year in both BM and circulation, and were also still largely connected to clones found in this population of CD27-IgD- cells, a trait that was unique to this population among all other analyzed cell populations. Somatic mutation analysis shows that these cells can be identified on distal branches of phylogenetic trees with ASC involvement and may serve as a reservoir of memory cells in the bone marrow following maturation of autoreactive clones.

#28 (morning session)

Phenotypic characterization of plasma cell subsets in systemic lupus erythematosus patients

Hong SH, Lee FE, Sanz I

Systemic lupus erythematosus (SLE) is severe systemic autoimmune disease with multiple clinical manifestations. It is characterized by multiple B cell abnormalities and production of variety of autoantibodies directed against nuclear, cytoplasmic and cell surface auto antigen. In the normal, non-disease state, the frequency of circulating plasma cells (PCs) is quite low and increases in a tightly regulated manner following vaccination or infection. However, in active SLE, the presence of PCs is deregulated with persistent appearance of increased number of PC in the circulation. The frequency of circulating PCs correlates with disease activity, as measured by the SLEDAI scoring system. Despite the important of pathogenic role of PCs in SLE, the properties of PCs still remained to be identified with respect to exact phenotype, location or longevity. In this study we found that frequency of circulating CD19-CD38hiCD138+ and CD19-CD38hiCD138- PC subset was significantly increased in active and flaring SLE patients as compared to vaccinated healthy controls and proportion of these CD19-PC subsets in total PCs was also increased in both active and inactive patients. Interestingly, 50-40 % of circulating PCs was Ki-67 negative in inactive SLE patients while most post-vaccination PCs are Ki-67 positive. CD19-CD138+ and CD19-CD138-PCs from SLE patients have large vacuoles, a feature observed in long-lived PCs in bone marrow and displayed lower level of HLA-DR. Thus, these data support that CD19-CD138+ PCs in SLE patients are partially similar to mature bone marrow PCs. These finding will provide a novel insight into characteristic feature of the SLE PCs.

#34 (afternoon session)

Uncovering the mechanisms by which Poldip2 regulates Rho GTPase signaling

Huff LP, Kikuchi DS, Griendling KK

NADPH oxidase (Nox) signaling in vascular smooth muscle cells (VSMCs) plays a vital role in cardiovascular function. Upon interaction with p22phox and/or other regulatory molecules, Noxes generate reactive oxygen species (ROS). Activity of Nox4, a dominant homolog in VSMCs, is enhanced by Polymerase delta-interacting protein 2 (Poldip2). Poldip2 also activates the Rho GTPase RhoA but the mechanism is unknown. RhoA is activated by guanine nucleotide exchange factors (GEFs). Using nucleotide-free RhoA to pulldown active

RhoGEFs we found that the RhoGEF, Epithelial cell transforming sequence 2 (Ect2), is activated by Poldip2. Overexpression of p22phox also enhances Ect2 activity, but neither Poldip2 nor p22phox activated Ect2 after treatment with the anti-oxidant N-acetyl cysteine. This suggests that Poldip2 activates Ect2 through a ROS-dependent mechanism. Surprisingly, Nox4 is not required for Poldip2- or p22-driven Ect2 activation, as Nox4-/- VSMCs behaved similarly to WT. To determine if the activation of Ect2 could be due to an interaction with Poldip2, we performed a co-immunoprecipitation, but no interaction was observed. To further characterize this process, we performed a fractionation and found that Poldip2 increases Ect2 activity in the nucleus. Because Ect2 has been shown to enhance SRF-driven transcription, we knocked down Ect2 and examined the expression of markers of differentiated VSMCs, which are regulated by SRF. Upon Ect2 knockdown we observed a decrease smooth muscle α -actin but not calponin. Our work begins to define a more unified picture of Nox and Rho signaling in VSMCs.

#38 (afternoon session)

Differences in longitudinal aortic hemodynamics of men and women as measured by phase contrast MRI

Iffrig E, Oshinski JN, Taylor WR

Numerous studies have demonstrated the pro-inflammatory property of low and oscillatory wall shear stress. WSS is the force exerted on a conduit wall (the endothelial layer in the case of the vascular system) by a viscous liquid. Areas of this disturbed wall shear stress correlate strongly with regions of atherosclerosis and vascular pathology such as the abdominal aorta. Given that men develop abdominal aortic disease more often than women, we hypothesized that there is a difference in the flow waveforms in the abdominal aorta leading to a difference in shear. To test this hypothesis we recruited 14 women and 9 men, aged 30-42 who were free of any cardiovascular disease. Using phase contrast MRI we calculated the longitudinal flow waves at 10 evenly spaced locations along the length of the aorta. Using a two-tailed t-test, we found that there was no significant difference in forward flow between men and women (5.46 ± 1.82 vs 4.43 ± 1.41 mL, $p > 0.05$) when averaging over the entire aorta. However there was a significant difference in reverse flow (0.75 ± 0.50 vs 0.27 ± 0.27 mL, $p < 0.01$) with men exhibiting a higher degree of flow reversal. Using a method developed in our lab, we found that there was a significant increase in the Oscillatory Shear Index (negative shear stress normalized to total shear) in men (0.40 ± 0.041 vs 0.35 ± 0.043 , $p < 0.05$). Additionally, we determined no difference in the time-averaged wall shear stress (1.83 ± 1.03 vs 2.78 ± 1.06 , $p = 0.06$). These results align with our hypothesis as they demonstrate differences in aortic hemodynamics between men and women.

#24 (morning session)

Decreased expression of negative regulators of Toll-like receptor signaling and increased TLR7 responsiveness in expanded IgD- CD27- B cells from systemic lupus erythematosus patients

Jenks SA, Marigorta U, Barwick B, Sanz I

B cell homeostasis is perturbed in SLE patients; in particular many patients with active disease have a large expansion of IgD- CD27- B cells (DN). The DN population is heterogeneous for CXCR5 expression, and CXCR5- DN are the majority population in SLE patients with expanded DN but not in HCD. To further understand how these expanded cells differ from other B cell subsets and how they may be dysregulated in SLE, we analyzed gene transcription through RNA sequencing of sorted purified naive, switched memory (SWM), CXCR5+ DN and CXCR5- DN (DNN) B cells from HCD and SLE patients with expanded DNN. DNN showed a pattern of gene expression, including specific transcription factors, that clearly differentiated them from naive B cells and memory B cells. Significantly, a negative regulator of TLR signaling, TRAF5, was uniquely down regulated in DNN in both HCD and SLE patients. Consistent with decreased expression of negative regulators of TLR signaling, DNN had enhanced in vitro sensitivity to TLR7 antagonist R848 as measured by ERK phosphorylation. Furthermore, R848 increased expressions of genes necessary for antigen presentation including HLA-DR and CD86 but decreased expression of the inhibitory receptors CD32b and CD72 in DN B cells but not naive B cells. These data demonstrate that DNN represent a separate B cell lineage with a distinct origin and function that likely play an important role in SLE pathogenesis through linking innate TLR signaling with B cell mediated adaptive immunity.

#21 (afternoon session)

Epidemiology and risk factors for fluconazole resistance and mortality among adults with candidemia in Atlanta and Baltimore

Kabbani S, Stein F, Ahlquist-Cleveland A, Hollick RA, Lockhart SR, Lyon GM, Chiller T, Harrison LH, Farley MM

Background: The impact of fluconazole resistance on candidemia mortality, a leading cause of bloodstream infections, remains poorly defined.

Methods: Population-based surveillance for candidemia was conducted in Atlanta and Baltimore. Case-isolates were sent to CDC for speciation and susceptibility testing. Risk factors associated with fluconazole resistance and all-cause mortality were identified using logistic regression in patients with incident candidemia.

Results: 3,553 cases of candidemia were identified between 2008-2013, average yearly incidence was 18.9 cases/100,000; 21.1% died. Overall, 6.9% of case-isolates were resistant to fluconazole, 26.6% of cases with fluconazole resistance died. Black race (adjusted odds ratio: 1.5; 95% confidence interval:

[1.0-2.1]), prior azole exposure (3.9; [2.7-5.8]), HIV infection (2.8; [1.7-4.8]), hematological malignancy (3.6; [2.0-6.4]), and solid organ transplant (3.0; [1.4-6.6]) were associated with fluconazole resistance. Chronic liver disease (0.4; [0.2-0.8]) was associated with decreased fluconazole resistance. Mortality risk factors included: age ≥ 65 years (1.7; [1.4-2.1]), malignancy (1.7; [1.3-2.2]), chronic liver disease (1.7; [1.3-2.4]), HIV infection (1.6; [1.1-2.5]), hospital onset infection (1.9; [1.4-2.5]), ICU admission before candidemia (3.6; [2.7-4.7]), treatment with amphotericin B (2.8; [1.7-4.5]), and infection with *C. tropicalis* (1.7; [1.2-2.4]). Treatment with any azole (0.5; [0.4-0.6]) and the removal of a central venous catheter (CVC) (0.4; [0.3-0.5]) were associated with lower odds of mortality in this model. No association was found between fluconazole resistance and mortality.

Conclusions: Risk of fluconazole resistance was greatest in immunocompromising conditions and with prior azole exposure. Mortality was highest in the elderly, with certain underlying diseases and in nosocomial disease, but was not associated with fluconazole resistance.

#34 (morning session)

Identification of CD4+ T Follicular Helper cell (TFH) response in blood after smallpox vaccination

Kabbani S, Lai L, Xu Y, Bailey A, Hartwell B, Anderson EJ, Roupael N, Edupuganti S, Kelley C, Camacho-Gonzalez A, Wrammert J, Jackson, L, Mulligan MJ

Background: TFH cells are germinal center T-cells involved in generating antibody (Ab) responses, express molecules that provide critical help for differentiation and maturation of B-cells, and correlate with functional Ab titers. A recent clinical trial of IMVAMUNE[®], derived from the Modified Vaccinia Ankara (MVA) strain, provided a unique opportunity to further our understanding of the role of TFH cells in a primary vaccine response.

Methods: Study participants received vaccine at days 1 and 29. Phenotypic characterization (CD4+CXCR5+CXCR3+ICOS+) of blood TFH cells was performed at days 1, 8, 15, 29, 36, 43 and 57. Pearson correlation with plasmablast response (CD3+CD20loCD19+CD38hiCD27 hi) is reported. Antigen-specificity and function of the blood TFH cells were assessed by intra-cellular cytokine staining (ICS) for IL-2, IL-4, IL-21, IFN- γ , and CD154 after ex vivo stimulation with MVA.

Results: Among 35 participants, IMVAMUNE vaccination stimulated a mean 3.5 fold increase of blood TFH cells that peaked at day 7 after priming. TFH expressed typical markers (Ki67 and PD1). TFH increase correlated with plasmablast increase (p-value=0.004). After boosting mean blood TFH increase was less (mean 2 fold). CD4+ cells expressed multiple cytokines after antigen-specific stimulation as measured by ICS, including typical TFH cytokines IL21 and IL4 that peaked at day 29.

Conclusions: Primary immunization with IMVAMUNE induced TFH cells in the peripheral blood, correlated with plasmablast response, and exhibited antigen-specific function. Blood TFH could serve as an early biomarker of an effective immune

response. Correlations with PRNT50 and ELISA titers are underway.

#49 (afternoon session)

PPAR γ activation attenuates ET-1 expression and endothelial dysfunction by inhibiting miR-27a in sickle cell mice lungs and hemin-treated HPAECs

Kang BY, Kleinhenz JM, Murphy TC, Sutliff RL, Archer D, Hart CM

Rationale: Pulmonary hypertension (PH), a serious complication of sickle cell disease (SCD), causes significant morbidity and mortality. Hemoglobin and free heme released during hemolysis induce endothelial dysfunction and may contribute to PH pathogenesis.

Objective: To examine these pathways in SCD-PH, we hypothesized that increased levels of miR-27a reduce PPAR γ expression leading to increased ET-1 expression, endothelial dysfunction, and SCD-PH.

Methods and Results: Townes sickle cell (SS) mice spontaneously developed PH and right ventricular hypertrophy. Levels of miR-27a, ET-1, endothelial specific markers, and ETS1 were increased in the lungs of 8-10 week old SS compared to littermate control (AA) mice whereas PPAR γ levels were reduced. In parallel studies, 8-10 week old SS or AA mice were gavaged with rosiglitazone (RSG, 10 mg/kg/d) or vehicle for 10 days. RSG attenuated reductions in PPAR γ and increases in miR-27a and ET-1 in SS mouse lung. In vitro, human pulmonary artery endothelial cells (HPAECs) were treated with DMSO or hemin (5 μ M) for 72 hours. Hemin increased miR-27a, ETS1, ET-1, and endothelial dysfunction, and reduced PPAR γ expression. These alterations were attenuated by treatment with RSG (10 μ M) during the last 24 hours of hemin treatment. Similarly, inhibition of miR-27a or overexpression of PPAR γ attenuated hemin-induced ET-1 and endothelial dysfunction. ETS1 knockdown attenuated increases in miR-27a and ET-1 expression and increased PPAR γ levels in hemin-treated HPAECs.

Conclusion: Collectively, these findings suggest that miR-27a reduces PPAR γ thereby increasing ET-1 and endothelial dysfunction and that PPAR γ activation may represent a novel therapeutic approach in SCD-PH pathogenesis.

#9 (morning session)

Barriers to effective prevention: applying a PrEP care continuum to a US cohort of black and white MSM

Kelley CF, Kahle E, Siegler A, del Rio C, Sanchez TS, Sullivan PS, Rosenberg ES

Introduction: Reductions in HIV incidence with pre-exposure prophylaxis (PrEP) for men who have sex with men (MSM) will require significant coverage of those at risk. We propose a simplified framework to achieve protection from HIV with PrEP: 1. At-risk MSM; 2. Aware of/willing to take PrEP; 3. Access to healthcare; 4. Receiving a PrEP prescription; and 5. Adhering to

PrEP. We evaluated the PrEP Care Continuum to a cohort of MSM and projected how many might achieve protection from HIV.

Methods: Involvement was an HIV incidence cohort of 562 black and white HIV-negative MSM in Atlanta, Georgia conducted from 2010-2014 with 32 observed HIV seroconversions, and which was used to apply the PrEP Care Continuum under optimistic estimates. Proportions with 95% confidence intervals (CI) of MSM in the total cohort and seroconverters projected to reach each step were calculated.

Results: Awareness/willingness was estimated at 50% for both analyses. Sixty-five percent of MSM in the total cohort, and 43% of seroconverters had health insurance; an additional 20% were ACA eligible in both groups. Sixty-nine percent of MSM in the total cohort and 75% of seroconverters met PrEP eligibility guidelines. The PrEP Care Continuum resulted in 15% (84/562; CI 12, 18%) of the cohort and 13% (4/32; CI 1, 23%) of seroconverters achieving theoretical protection from HIV.

Conclusions: Even with generous, 'best-case scenario' estimates, few Atlanta MSM will achieve protection from HIV with PrEP. Novel strategies for PrEP delivery are needed to achieve the necessary effectiveness for MSM at risk of HIV.

#49 (morning session)

The associations between vitamin D and hospitalizations with and without an infection: a national cohort of Medicare beneficiaries

Kempker JA, Magee MJ, Cegielski JP, Martin GS

Research has implicated low 25-hydroxyvitamin D [25(OH)D] as a risk factor for infection; however, results have not been consistent. To further determine this relationship we conducted a cohort study using Medicare beneficiaries participating in the 2001-2004 National Health and Nutrition Examination Surveys (NHANES) with data individually linked to hospital records from the Centers for Medicare and Medicaid Services. The primary exposure was a 25(OH)D < 15 ng/mL vs. 25(OH)D ≥ 15 ng/mL. The outcomes were a hospitalization with or without an infection within 1 year from the NHANES survey, determined from the final ICD-9-CM discharge codes. Of 1,713 individuals, 20% had a baseline serum 25(OH)D < 15 ng/mL, 77 individuals experienced a hospitalization with an infection and 287 experienced a hospitalization without infection. In multivariable analyses, a serum 25(OH)D < 15 ng/mL was associated with a higher risk of a hospitalization with an infection (risk ratio (RR) 2.8, 95% confidence interval (CI): 1.3, 5.9, P<0.01), but not of a hospitalization without an infection (RR 1.4, 95% CI: 0.9, 2.1, P=0.1).. This study demonstrates a significant association between a serum 25(OH)D concentration < 15 ng/mL and the subsequent risk for hospitalization with an infection among Medicare beneficiaries.

#3 (morning session)

Disparities in pancreatic cancer: our experience in an urban African-American cohort

Khan TA, Liu J, Russell MC, Chawla S

Objective: Pancreatic adenocarcinoma is the fourth leading cause of cancer-related deaths in the US. African-Americans (AA) are frequently underrepresented in large databases even though they are known to have higher incidence and mortality from pancreatic cancer. We examined the clinical presentation and treatment paradigms in a cohort of AA patients presenting to Grady Memorial Hospital (GMH) and compared them to those from large national databases.

Methods: A retrospective chart review identified patients diagnosed with pancreatic adenocarcinoma between 2008-2013. Data analyzed included age at diagnosis, gender, race, comorbidities, tobacco and/or alcohol use, insurance status, tumor stage, treatment received, and surgery performed.

Results: 119 AA patients were identified. The median age of diagnosis was 60, compared to the national median of 71 (p<0.05). 68% of our AA patients presented at Stage III/IV, compared to the national average of 61% (p<0.05). 64% of our patients did not receive any treatment. Definitive surgery was only offered to 10 % of patients. 45% of the patients in our AA patient cohort were <60 yo. When dichotomizing age to >60 or ≤60 yo, multivariate analysis revealed diabetes and smoking history to have a significant association with pancreatic cancer in younger patients.

Conclusions: AA patients at GMH present with more advanced pancreatic cancer at a younger age and are less likely to receive treatment than previously reported. Smoking and diabetes remain significantly associated with pancreatic cancer in young AA. Disparities in treatment may be related to socioeconomic and cultural factors that should be further investigated.

#17 (afternoon session)

Repeat outpatient endoscopy is suboptimal in patients discharged from an academic medical center

Klimenko M, Iskandar H

Introduction: In this project we aimed to determine the frequency of completion of indicated repeat outpatient endoscopy after discharge in an academic center.

Methods: We conducted a retrospective review of inpatients undergoing endoscopy at a teaching hospital between 9/1/2014-10/31/2014. Medical records were reviewed to determine whether repeat endoscopy was indicated. Indications for repeat endoscopy were: LA Class C or D esophagitis (ASGE guideline, 2015), un-biopsied gastric ulcers (ASGE guideline, 2010), and incidental colonic polyps left in place. If repeat endoscopy was indicated, we determined if follow-up endoscopy was recommended at discharge, and whether it was performed.

Results: 124 inpatient endoscopies were reviewed. Mean age: 54 ± 2 years, 54% female, 47% white, 45% African American, and 8% other. Repeat endoscopy: Indicated in 28 patients (6 for esophagitis, 12 for gastric ulcers, 8 for colon polyps, 1 for peptic stricture, 1 for poor prep). Of these 28 patients, 14 had repeat endoscopy recommended on discharge (3 for esophagitis, 8 for gastric ulcers, 1 for peptic stricture for dilation, 1 for colon polyps, and 1 for poor prep). Recommended repeat interval was 4-6 weeks in 5 patients, 6-8 weeks in 7 patients, and not specified in 2 patients. At 6 months after discharge, 4 patients completed repeat endoscopy. None of the 14 patients had significant comorbidities that may have delayed follow-up. 7/14 patients were seen in GI clinic.

Discussion: Follow-up endoscopy completion in the transition from inpatient to outpatient care is suboptimal. This is an important target for future quality improvement initiatives.

#39 (afternoon session)

The matricellular protein Periostin (POSTN) is required for liver fibrillogenesis

Kumar P, Smith T, Rahman K, Thorn N, Chopyk DM, Anania FA

POSTN is a secreted 90kDa matricellular glycoprotein that is involved in embryologic development as well as in the pathogenesis of tumor development, asthma, and fibrosis. A recent manuscript demonstrated a novel role for POSTN in hepatic fibrogenesis since POSTN global null mice failed to develop significant liver scar following carbon tetrachloride (CCl₄) gavage. Here we provide a mechanistic explanation as to how POSTN functions as an extracellular matrix (ECM) scaffolding and regulatory protein, in contrast to the fibrillar collagens, which are key structural molecules of the dense ECM. In vitro studies were conducted with primary cultured rat hepatic stellate cells (HSCs) exposed to 100 ng/ml POSTN in which antibodies against alpha V beta 3 integrin blocked activation of focal adhesion kinase (FAK) as assessed by phosphorylation of tyr576/577. We also demonstrated for the first time by immunoprecipitation of activated HSC lysate; and by binding assay that POSTN binds discoidin-domain receptor I (DDR-1). Si-SMAD2/3 blocked production of POSTN in activated HSCs, while POSTN increased transforming growth factor beta one mRNA expression suggesting a feedback loop. POSTN, is responsible for increased lysyl oxidase activity, resulting in collagen extensive cross-linking. Sirius Red staining revealed in POSTN global KO mice significant absence of dense collagen fibrils when compared to WT mice all gavaged with CCl₄. By atomic absorption spectroscopy liver stiffness in kiloPaschals was also significantly lower in POSTN global KO mice than in WT mice that underwent gavage. POSTN is a major player in maintenance of ECM stiffness and mechanics in liver fibrosis.

#50 (afternoon session)

Knockdown of mechanosensitive miRNA cluster—miR-106b-25 decreases endothelial proliferation and prevents atherosclerosis in ApoE-/- mice

Kumar S, Kim CW, Jo H

Atherosclerosis is the underlying cause of cardiovascular events, such as heart attack and stroke. It preferentially occurs in arterial regions exposed to disturbed flow (d-flow), in part, due to alterations in endothelial gene expression. Emerging evidence indicates that alteration of flow conditions regulate expression of small, noncoding RNAs (miRNAs) in endothelial cells. Here, using a partial carotid ligation model of d-flow induced atherosclerosis, we identified a highly conserved, flow-sensitive miRNA cluster, miR-106b-93-25, that is upregulated in the carotid endothelium that experienced d-flow for 48 hours. Additional studies using endothelial-enriched RNAs from the lesser- (chronic d-flow region) and greater curvature (chronic s-flow region) of aortic arch further validate the increased expression of 106b-93-25 in the chronic d-flow regions. Using arterial endothelial cells from human and mouse and a cone-and-plate shear device, we found that expression of miR-106b-93-25 increases in the endothelial cells exposed to oscillatory shear stress for 24 h. In silico and subsequent wet-lab target identification studies showed that this miRNA cluster targets the inhibitors of cell cycle regulators, cyclin-dependent kinase inhibitors (CDKIs). Using gain-of-function (pre-miR-106b, -93 and -25) and loss-of-function (anti-miR-106b, -93 and -25) approaches, we found that this miRNA cluster downregulates the CDKN1A and CDKN1B in a flow-dependent manner. Using our mouse partial carotid ligation model of d-flow induced atherosclerosis, we demonstrated that genetic knockdown of mechanosensitive miRNA cluster—miR-106b-25 using heterozygous miR-106b-25+/- mice on ApoE background prevents atherosclerosis. Our results suggest that targeting mechanosensitive miRNA cluster using anti-miRNA-based approaches may provide a new treatment strategy for atherosclerosis.

#48 (morning session)

MF59 significantly increases H7N9 avian influenza vaccine-induced blood TFH cells and enhances functional antibody responses

Lai L, Xu Y, Mask K, Beck A, Colwell J, Rimman N, Turner PL, Wang D, Edupuganti S, Roupheal N, Anderson E, Spearman P, Mulligan MJ

Background: Antibody responses require CD4+ helper T cells, particularly T follicular helper cells (TFH), which express chemokine receptor CXCR5 for homing to the lymphoid follicles and instruct germinal center (GC) formation and subsequent memory antibody responses. Approximately 10%-15% of blood CD4+ T cells in humans express CXCR5 and thus could provide a window for investigating GC TFH in the clinical setting.

Methods: Thirty-six healthy adult participants received 2 doses of influenza A/Shanghai/2/13 (H7N9) inactivated virus vaccine on days 0 and 21 with or without MF59 adjuvant. Blood TFH,

memory B cell, HAI, and NAb responses were measured at serial time points.

Results: We found blood TFH cells (defined as ICOS+CXCR3+CXCR5+CD4 cells) emerging mainly at day 7 after vaccination, and co-expressing PD-1/Ki-67/IL-21. These cells were H7N9-specific and induced autologous memory B cells to differentiate into plasma cells. Induced blood TFH cells at day 7 were significantly higher ($P=0.003$) in vaccinees that received MF59 at day 0 ($N=22$) compared to those who did not receive MF59 ($N=14$). In addition, blood TFH correlated with HAI ($P=0.012$) and Nab ($P<0.001$) antibody titers and memory B cell responses ($P=0.003$).

Conclusions: Our study revealed a previously unappreciated aspect of the oil-in water adjuvant MF59 to improve the immune response in the setting of H7N9 vaccine by increasing blood TFH cell response that correlated with subsequent HAI, NAb, and memory B cell responses. This could be useful as a biomarker of an early effective immune response.

#29 (morning session)

Identification of long-lived plasma cells in human bone marrow

Halliley JL, Tipton C, Liesveld J, Rosenberg AF, Darce J, Gregoretti IV, Popova L, Kaminiski D, Fucile CF, Albizua-Santin I, Kyu S, Chiang K-Y, Bradley KT, Burack R, Slifka M, Hammarlund E, Wu H, Zhao L, Walsh EE, Falsey AR, Randall TD, Cheung WC, Sanz I, Lee FE

Antibody responses to viral infections can be sustained for hundreds of years by long-lived plasma cells (LLPCs). However, LLPCs have yet to be characterized in humans. Here we used CD19, CD38 and CD138 to identify 4 distinct PC populations in the human bone marrow (BM). We show that the CD19-CD38hiCD138+ fraction is morphologically distinct and represents the exclusive repository of PCs specific for viral antigens to which the subjects had not been exposed for more than 40 years. We also show that protein sequences of purified measles- and mumps-specific circulating antibodies are encoded exclusively by the BM CD19-CD38hiCD138+ PCs. Additionally, reconstitution of the monoclonal antibody from the BM PC RNA sequence demonstrates mumps specificity. Finally, Next Generation Sequencing (NGS) identifies a distinct VH repertoire of the CD19-CD38hiCD138+ subset that is relatively uncoupled from other BM PC subsets, suggesting that this compartment represents the B cell response's "historical record" of antigenic exposure. Combined, our studies provide original evidence for a bone fide, discrete long-lived plasma cell compartment within the human BM.

#52 (afternoon session)

Impaired functional sympatholysis in end-stage renal disease

Lee HL, DaCosta D, Park S, Liao P, Park J

End-stage renal disease (ESRD) patients have an exaggerated increase in blood pressure during both static and rhythmic

handgrip exercise, contributing to exercise intolerance in these patients. The increase in blood pressure during exercise is largely due to an increase in reflex sympathetic nervous system (SNS) activation; however, vasoconstriction within the exercising skeletal muscle is prevented due to local vasodilatory forces in order to preserve blood flow, termed functional sympatholysis. We hypothesized that ESRD patients have impaired functional sympatholysis, which contributes to the exaggerated exercise pressor response and exercise dysfunction. We tested this hypothesis by measuring change in muscle oxygenation (tissue saturation index, TSI) using near infrared spectroscopy during sympathetic activation induced by lower body negative pressure (LBNP) alone, and during LBNP with concomitant handgrip exercise. The difference in muscle oxygenation (TSI) during LBNP alone to LBNP with concomitant handgrip exercise represents functional sympatholysis. There was a significant difference in the change in TSI during LBNP alone and during LBNP with concomitant handgrip exercise between the ESRD and control groups ($p=0.025$). While control subjects have a significant attenuation in the decrease in muscle TSI from LBNP alone to LBNP with concomitant handgrip exercise ($p=0.017$), ESRD patients have no significant improvement in muscle oxygenation during LBNP with concomitant handgrip exercise compared to LBNP alone ($p=0.210$). These results suggest that ESRD patients have impaired functional sympatholysis, which could contribute to the augmented exercise pressor response and exercise intolerance in these patients.

#40 (afternoon session)

Continuous PTH treatment induces bone loss through AlphaS signaling in T cells

Li JY, Robinson J, Adams J, Weitzmann MN, Pacifici R

Hyperparathyroidism in humans and continuous PTH treatment (cPTH) in mice cause bone loss by regulating RANKL production by osteocytes and osteoblasts. T cells markedly potentiate the bone catabolic effect of cPTH by secreting the osteoclastogenic cytokine TNF, a factor required for cPTH to expand Th17 cells and induce IL-17 production. IL-17 is an upstream cytokine that induces RANKL production by osteocytes and osteoblasts. PTH binding to its receptor PPR activates G protein alpha (GalphaS). Activation of GalphaS has been shown to induce the differentiation of Naive CD4+ cells into Th17 cells. To investigate if cPTH upregulates Th17 differentiation by activating GalphaS in naive CD4+ T cells, we utilized GalphaS Δ CD4,8 mice lacking GalphaS expression in T cells. In vivo cPTH treatment increased the number of BM Th17 cells and the loss of cortical and trabecular bone in GalphaS fl/fl mice, but not in GalphaS Δ CD4,8 mice. Signaling events downstream of GalphaS include cAMP generation and activation of L-type calcium channels. The latter contributes to Th17 cell differentiation. To determine if Ca²⁺ influx is required for Th17 cell expansion induced by cPTH, we fed mice with water with or without the L-type calcium channel blocker diltiazem and infused them with vehicle and cPTH. Diltiazem blocked the increase in the number of BM Th17 cells, and the loss of cortical and trabecular bone induced by cPTH. In summary, these findings demonstrate that cPTH causes bone loss by expanding Th17 cells via GalphaS/cAMP/Ca⁺⁺ signaling.

Calcium channel blockers may thus represent novel therapeutic strategies for hyperparathyroidism.

#28 (afternoon session)

In the setting of abdominal aortic aneurysm formation, catalase expression is down regulated via a PGC1 α -mediated signaling pathway

Liu Y, Weiss D, Joseph G, Taylor WR

Introduction: It was demonstrated that catalase expression is down-regulated in the AAA disease process. In addition, a reduction in catalase activity and subsequent increase in H₂O₂ are functionally linked to AAA formation. It has also been shown that angiotensin II stimulation causes a reduction in catalase expression via a PGC1 α -mediated mechanism in-vitro. Thus, it is hypothesized that in the setting of AAA formation, catalase expression is down-regulated via a PGC-1 α -mediated signaling pathway.

Method: Two complementary animal models of AAA formation were utilized. Laparotomies and peri-aortic application of CaCl₂ or elastase are carried out in C57/BL6 mice. Aortas were harvested at different time points for analysis. In the future, we will employ either a murine SMC-specific knockout model of PGC-1 α to perform loss of function studies or over-express catalase in the model to observe the impact of the pathway on AAA pathogenesis.

Results: Thus far, we have observed that all elastase treated mice had increased in aorta diameter over 50% two weeks after the treatment. Histology studies confirmed destructed tunica media and inflammatory infiltrations in the abdominal aortas. Catalase expression was down-regulated in addition to up-regulation of several prototypical inflammatory markers. MMP expressions was also gradually increased over time in the model. Complementary data was seen in the CaCl₂ treated animals. Future studies will help to define the role of PGC-1 α .

#35 (afternoon session)

The role of human osteopontin isoforms in collateral formation

Caroti C, Harirforoosh S, Joseph G, Weiss D, Vereen J, Taylor WR, Lyle AN

Coronary and peripheral artery diseases lead to impaired blood flow and ischemia, initiating processes that promote neovascularization to restore blood flow and preserve tissue function. We previously demonstrated that osteopontin (OPN), a matricellular cytokine, is critical to collateral formation in response to ischemia. Humans express three OPN isoforms (a, b, and c), which are differentially upregulated in various diseases; however, the roles of these isoforms in neovascularization and cell migration remain undefined. This study aims to define the differential effects of human OPN isoforms on collateral formation in vivo and to investigate the mechanisms by which human OPN isoforms exert these effects. To assess how human OPN isoforms affect neovascularization, we used a murine model of hind limb ischemia in OPN^{-/-} mice.

Mice received adductor intramuscular injection of 1.5x10⁶ lentivirus particles expressing OPNa, OPNb or OPNc at time of hind limb surgery. Treatment with OPNa or OPNc significantly improved limb perfusion and restored functional limb use, as assessed by voluntary running wheel use, compared to OPNb and control treated animals. These effects of OPN isoforms on neovascularization were not due to differences in expression levels. Results demonstrated that isoforms differentially affect capillary density, inflammatory and smooth muscle cell infiltration, and mRNA expression levels of several pro-arteriogenic factors. Isoform effects on vascular volume, density, connectivity and diameter are being assessed using Micro-CT angiograms. In conclusion, human OPN isoforms differentially regulate collateral vessel formation and may represent potential new therapeutic targets to promote neovascularization and preserve function in ischemic vascular disease patients.

#12 (afternoon session)

False positive rates of atrial fibrillation detection among stroke patients who receive Medtronic implantable loop recorders

Maddox S, Hoskins M, Rangaraju S, Henriquez L, Davis B, Nahab F

Introduction: Atrial fibrillation is a known risk factor for the development of stroke. Implantable loop recorders (ILRs) have algorithms to detect occult atrial fibrillation and can be used in patients with cryptogenic stroke. There is limited data on the frequency of false positive atrial fibrillation detected by the Medtronic ILR.

Hypothesis: Medtronic ILRs have a high rate of false positives but are still effective at detecting atrial fibrillation in patients with cryptogenic stroke.

Methods: All stroke patients who underwent ILR placement from Jan 1, 2013 to June 30, 2015 were prospectively collected through an administrative database. Baseline and clinical characteristics were retrospectively obtained. A random sampling of ILR tracings identified as atrial fibrillation by the Medtronic algorithm was adjudicated by a board certified electrophysiologist for accuracy.

Results: Among 52 patients with a history of ischemic stroke or TIA there were 166 rhythm strips identified as atrial fibrillation by the Medtronic algorithm which were adjudicated. Of the 166 strips reviewed, 140 (84%) were incorrectly identified as atrial fibrillation. Of the 38 (73%) patients who had ILR implantation for cryptogenic stroke, 4 (11%) were identified as having true atrial fibrillation by ILR and adjudication over 413 patient-months of monitoring; mean time to atrial fibrillation detection was 93 days after implantation.

Conclusions: Stroke patients who undergo Medtronic ILR placement have high false positive rates of atrial fibrillation detected with the Medtronic algorithm. When reviewed by a trained cardiologist for accuracy, the Medtronic ILRs remain effective at detecting atrial fibrillation in cryptogenic stroke patients.

#32 (morning session)

Systemic lupus erythematosus specific antibody class present in subset of schizophrenia patients

Marcus JE, Jenks SA, Belledent D, Cashman KS, Pearce B, Duncan E, Yu R, Sanz I

Antibodies encoded by the VH4-34 heavy chain, recognized by the rat anti-human idiotype 9G4 (9G4+) are autoreactive and in healthy subjects are prevented from class switching to IgG due to tolerance mechanisms in the germinal center. In systemic lupus erythematosus (SLE), this tolerance is lost and these 9G4+ antibodies are allowed to class switch to IgG. This study investigates whether class switching of 9G4+ antibodies to IgG could be contributing to schizophrenia, a neuropsychiatric disorder associated with autoimmunity and the presence of various autoantibodies. Our study found 2/29 patients with schizophrenia had elevated 9G4+ IgG titers at concentrations similar to SLE, while none of the 39 healthy controls or 14 family members of schizophrenics had elevated antibody levels. Interestingly, none of the schizophrenic patients were positive for 9G4+ IgM. To see if this was a more general process in autoimmune or inflammatory neurologic disorders, samples were obtained from patients with Guillain-Barre, chronic inflammatory demyelinating polyneuropathy, and amyotrophic lateral sclerosis. Of these neurologic disorders, only one sample tested positive for IgM and no samples positive for IgG. These results favor a more disease-specific role of 9G4+ IgG to schizophrenia rather than a generalized process in inflammatory neurologic disorders. This study is the first to show 9G4+ IgG antibodies in a neuropsychiatric disorder and provides further evidence of immune dysfunction in schizophrenia.

#39 (morning session)

A prime boost immunization regimen based on a SAd36 vectored multi-stage malaria vaccine induces protective immunity

McCaffery JN, Fonseca JA, Cabrera-Mora M, Dmitriev I, Curiel D, Moreno A

In 2013 there were an estimated 198 million cases of malaria and 584,000 deaths, 78% of which occurred in children under 5 years, making malaria a leading cause of death in children of this age. A malaria vaccine, capable of producing a balanced cellular and humoral immune response, is needed to reduce the burden of this disease in the areas where access to medication is logistically demanding. We have previously reported the design of a chimeric protein based on P. yoelii CSP and MSP1 antigens designated PyLPC-RMC. This construct is able to induce robust antibody and CD4 T cell responses. Based on the evidence that viral vectors increase CD8 T cell mediated immunity we tested heterologous prime-boost immunization regimens that include human adenovirus serotype 5 vectors (Ad5). While Ad5 remains a popular vector for vaccine studies, the high prevalence of pre-existing immunity to Ad5 severely compromises its utility. The use of non-human Ad species is an alternative to Ad5-based vaccination. Here we use simian adenovirus 36 (SAd36) as candidate for a vectored malaria vaccine since there is little to no

pre-existing immunity to this virus in human populations. Our studies show the induction of specific CD8 T cell response and similar antibody titers when compared to a prime-boost immunization regimen that includes Ad5PyLPC-RMC. This robust immune responses induced by SAd36PyLPC-RMC are translated into a lower parasite load and higher hemoglobin levels after a P. yoelii challenge when compared to naive and mice immunized with Ad5PyLPC-RMC.

#57 (morning session)

Non-indicated endoscopic retrograde cholangiopancreatography in suspected choledocholithiasis: prevalence, complication, and diagnostic yield

Mekaroonkamol P, Parikh M, Vora R, Berger S, Qayed E

Endoscopic retrograde cholangiopancreatography (ERCP) is the intervention of choice for patients with high risk for choledocholithiasis however, it is recommended to be deferred to magnetic resonance cholangiopancreatography (MRCP) when the risk is intermediate. This study aims to evaluate diagnostic yield and risk associated with the procedure when it is performed outside of the current guideline's recommendation. All ERCP performed after the publication of American Society of Gastrointestinal Endoscopy guideline for endoscopic evaluation of suspected choledocholithiasis in 2010 were reviewed. Majority of patients were African-American (73%) and female (76%). Out of 63 procedures performed for suspected choledocholithiasis, 9 (14%) were non-indicated according to the current guideline. All were performed for patients at intermediate risk. The reasons to proceed with ERCP without obtaining MRCP first were all because of surgeon's requests. Among non-indicated ERCPs, 67% found choledocholithiasis and successfully extracted them. There was no statistically significant difference between bilirubin level, common bile duct size, presence of biliary pancreatitis, age, race, gender, or body mass index of ERCP with positive and negative findings. Complication rate was 4.7%. All were post-ERCP pancreatitis except for one case of post-sphincterotomy bleeding. Even though 14% of ERCPs were non-adherent to the current guideline, there was a substantial yield of 67% from these "non-indicated" procedures. We found no predicting parameter of positive ERCP. However, the statistical analysis was likely underpowered. ERCP may be considered as an initial diagnostic modality in selected patients with intermediate risk. Its cost-effectiveness should be further assessed with procedural risk taken into consideration.

#15 (afternoon session)

Safety and efficacy of moderate sedation in obese patients undergoing endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis

Mekaroonkamol P, Parikh M, Vora R, Berger S, Qayed E

The most common indication for Endoscopic Retrograde Cholangiopancreatography (ERCP) is choledocholithiasis, a condition commonly affects obese patients, who are at risk of sedative complication. This study aims to evaluate the safety and efficacy of moderate sedation for obese patients undergoing

ERCP for suspected choledocholithiasis. A retrospective review of all ERCPs performed for suspected choledocholithiasis over a 45-month period was conducted. Out of a total of 63 ERCPs, 29 (46%) were performed for patients whose body mass index was more than 30 with 10 (16%) procedures were performed for morbidly obese patients. Majority of the population were African-American (86%) and female (90%) with a mean age of 36 year-old. Among ERCPs for obese patients, 55% were performed using moderate sedation with fentanyl or meperidine and midazolam, while the rest were performed under general anesthesia. There was no statistically significant difference in complication rate between the two methods (odds ratio 0.14; 95%CI 0.01-3.18, $p=0.22$). No sedative-specific complications were observed in both groups. The technical success rate was lower in moderate sedation group (62.5%) than general anesthesia group (92%) however, the difference was not statistically significant (OR 7.2; 95%CI 0.7-70.2, $p=0.08$). Reasons for failure were inability to cannulate (43%), inability to extract the stone (43%), and patient's intolerance to sedation (14%). Moderate sedation is a viable mean of sedation in obese patients undergoing ERCP. However, this study showed lower success rate compared to general anesthesia. We believe that inadequate sedation contributed to higher technical failure rate. Overall risk and complexity of the procedure need to also be considered to determine the proper method of sedation.

#41 (afternoon session)

Red blood cell microparticles from stored blood impair monocyte-endothelial adhesion

Mitchell AJ, Gray W, Rooney K, Mohamed I, Quyyumi A, Roback J, Searles C

Red blood cell (RBC) transfusions are known to modulate the immune system and may increase risk of infection. The mechanisms responsible for immune modulation remains unclear. RBC derived MPs (RMPs) accumulate during RBC storage and may interact with the endothelium upon transfusion. We hypothesized that endothelial cells internalize RMPs, delivering cargo and altering endothelial response to inflammation. RBC units were stored for 42-50 days and RMPs were isolated using differential centrifugation. RMPs were stained with Calcein-AM and incubated with human aortic endothelial cells (HAECs) for 24 hours. Cellular uptake of RMPs was assessed by flow cytometry and confocal microscopy. miRNA transfer was measured by qRT-PCR. The influence of RMPs on monocyte adhesion to endothelial cells was assessed using a static monocyte adhesion assay. Flow cytometry detected a marked increase in fluorescence from HAECs treated with calcein-labeled RMPs (MFI = 194.8) compared to controls (MFI = 3.2). Additional flow cytometric studies and confocal microscopy confirmed that the RMPs were internalized by HAECs rather than simply adhering to the cell surface. miR-451, an erythrocyte specific miRNA, increased ~500-fold HAECs after 2 hours of co-incubation. RMPs inhibited monocyte adhesion compared to control cells (67 ± 7 cells/LPF versus 153 ± 7 cell/LPF, respectively; $p = 0.002$). Co-treatment with RMPs and LPS blunted the increase in cell adhesion observed with LPS alone (225 ± 15 cells/LPF versus 388.5 ± 24 cell/LPF, respectively; $p = 0.004$). RMP induced changes in endothelial

phenotype represent a novel mechanism by which RBC transfusions have immunomodulatory effects.

#19 (morning session)

A mobile application to combat cardio metabolic syndrome

Mohamed Kelli H, O'Connor J, Mustafa M, Lattouf OM

Background: Mobile technology has become an essential part of daily living and mobile applications have the potential to impact healthcare delivery and education. This mobile application was created in order to help individuals to visualize metabolic health status in a simple and interactive way.

Methods: The App concept resulted from brainstorming sessions held at series of conferences on Cardio Metabolic Syndrome supported by multiple organizations including Emory University, Georgia Department of Public Health, Gulf Heart Association and the American College of Cardiology. The application algorithm was built based on the ATP-III metabolic syndrome definition in combination with major cardiovascular risk factors and consumer's demographics. It was programmed using the iOS 8.0 application user interface.

Results: By entering the individual's blood pressure, weight, height, blood glucose, cholesterol, and smoking history, the tool creates the easily understood and colorful diagram in the forms of a dart board or a "Bull's Eye" with 3 concentric circles. The outer circle is green (low risk; maintain a healthy lifestyle and regular checkups), and yellow in the middle (intermediate risk; seek lifestyle and medical attention soon), and innermost is red (high risk; seek medical advice). The user is able to save their overall score and track it over time.

Conclusions: The mobile application is intended to be an easy to access and simple tool to educate the public, improve population health, and provide individuals with information for self-risk assessment and accordingly to pursue life style behavioral modification and medical care when indicated.

#23 (afternoon session)

TGF β 1 regulates lung fibroblast-to-myofibroblast transdifferentiation by Thy-1 methylation

Neveu W, Mills S, Staitieh BS, Guidot D, Sueblinvong V

Rationale: Idiopathic pulmonary fibrosis is an interstitial lung disease that increases in incidence with age. Although the causative mechanisms remain unclear, there is compelling evidence implicating the pro-fibrotic cytokine TGF β 1 in its pathogenesis. We previously identified in senescent mice a pro-fibrotic lung phenotype of increased Thy-1 negative fibroblasts. As Thy-1 acts as a fibrotic suppressor and that loss of gene expression by epigenetic modification leads to lung fibroblast to myofibroblast transdifferentiation, we evaluated whether TGF β 1 regulates Thy-1 in mouse lung fibroblasts by promoter hyper-methylation.

Methods: Mouse lung fibroblasts were treated with TGF β 1 \pm the DNA methyltransferase (DNMT) inhibitor 5-AZA and analyzed for

Thy-1 gene and protein expression by quantitative RT-PCR and FACS analysis. DNMT expression was determined by RT-PCR and Western blot analysis. DNMT activity and Thy-1 promoter methylation were measured by ELISA and quantitative methyl PCR. Lastly, myofibroblast phenotype was evaluated in cells treated with TGF β 1± 5-AZA by RT-PCR and Western blot analyses of α -SMA expression.

Results: TGF β 1 reduced Thy-1 expression in mouse lung fibroblasts and co-treatment with 5-AZA ameliorated these effects. Analysis of the DNMT pathway suggested that TGF β 1 induced DNMT activation and caused Thy-1 promoter hypermethylation. Finally, TGF β 1-mediated Thy-1 methylation was sufficient to induce fibroblast-to-myofibroblast transdifferentiation.

Conclusions: These findings suggest that TGF β 1 epigenetically regulates fibroblast phenotype through modulation of Thy-1 and may increase lung susceptibility to the development of fibrosis. Our study raises the possibility that drugs that block methylation may be clinically useful in restoring Thy-1 expression and reversing the myofibroblast phenotype in lung fibrosis.

#48 (afternoon session)

Secretome of mesenchymal stromal cells supports human plasma cell survival

Nguyen DC, Kyu S, Galipeau J, Chiang KY, Waller E, Roberson J, Sanz I, Lee FE

Bone marrow (BM) long-lived plasma cells (PCs) are responsible for maintenance of life-long serological protection. As terminally differentiated cells, human PCs rapidly die in conventional ex vivo cultures. We co-cultured healthy human blood antibody secreting cells (ASCs) with BM-derived mesenchymal stromal cells (MSCs) or in the MSC secretome and performed ASC ELISpots and ELISAs. Similarly, we co-cultured BM PCs with MSCs or in the MSC secretome and assessed their survival and function by these assays. We found that MSC co-cultures supported ASC survival and function, shown by IgG and IgA secretion for 45 days. MSC co-cultures also supported BM PCs for 70 days. MSC-ASC or MSC-PC cell contact was not necessary to maintain this survival. Thus, we showed that the MSC secretome also maintained survival of both blood ASCs and BM PCs (for at least 31 days). Additional factors such as APRIL together with the MSC secretome enhanced the survival and function of blood ASCs compared to the MSC secretome alone. However, addition of IL-6, IL-5, IL-21, or Osteopontin to the secretome did not provide any additional survival advantage. Furthermore, the MSC secretome maintained survival and Ig secretion of single cell cultures of blood ASCs and BM PCs for 7 days. Finally, we demonstrated differential Ig secretion rates from circulating ASCs at steady state (167 ± 23 pg/cell/day) and after immune priming with vaccination (387 ± 65 pg/cell/day). In conclusion, we have identified a novel secretome from allogeneic human BM-derived MSCs that supports survival and maintenance of Ig secretion of human blood ASCs and BM PCs.

#50 (morning session)

Chlorhexidine-impregnated transparent dressing for prevention of catheter-related bacteremia in hemodialysis patients: a quality improvement study

Niyyar VD, Apata IW, Hanfelt J

Background: CRBSI are a major cause of morbidity in HD patients dialyzing with a CVC. A major route of catheter contamination is introduction of organisms from the skin to the catheter. Tegaderm-CHG is a transparent catheter dressing with an integrated gel containing chlorhexidine, designed to combine the benefits of transparent dressings; and the bactericidal and bacteriostatic benefits of chlorhexidine. We conducted a QI project to assess the rates of catheter-related bloodstream infection (CRBSI) in three dialysis units following the introduction of chlorhexidine-impregnated transparent catheter dressings.

Methods: Our study was conducted in two phases. In the first phase (9/12 through 10/13), we introduced the intervention, Tegaderm-CHG, to EDC, one of the three Emory hemodialysis units. EDGB and EDNS were the control sites where standard gauze catheter dressings were maintained. The rates of CRBSI at each dialysis units were compared during the 12-month intervention to the 12 month pre-intervention period. In the second phase of the study (11/2013), Tegaderm-CHG dressing was extended to EDGB and EDNS, while still being used at EDC.

Results: In phase 1, the catheter infection rate (per 1,000 catheter days) in EDC decreased by 51% (pre: 1.69, post: 0.82). The infection rates at EDGB and EDN decreased significantly in phase 2 by 86% (pre: 1.86, post: 0.26), and 53% (pre: 1.89, post: 0.88), respectively. At EDC, the catheter infection rate did not change significantly in phase 2.

Conclusions: The use of Tegaderm CHG dressing was associated with decreased rates of CRBSI at Emory outpatient dialysis units.

#7 (afternoon session)

The impact of acute kidney injury and stress hyperglycemia on inpatient mortality and hospitalization costs

Oyedokun F, Fayman M, Vellanki P, Zhao L, Alfa D, Robalino G, Cardona S, Pasquel FJ, Umpierrez GE

Acute kidney injury (AKI) and hyperglycemia are common complications during hospitalization. We analyzed the impact of AKI in non-diabetic patients with stress hyperglycemia (SH, blood glucose (BG) > 140 mg/dL) and diabetes (DM) on inpatient mortality and hospitalization costs at two Emory Hospitals. AKI was defined as an increase in serum creatinine > 1.5 mg/dl from the admission value between 1/2012 and 12/2013. Hospital costs were calculated using cost-charge ratios from Centers for Medicare & Medicaid Services. Among 35,431 patients, 10,139 (28.6%) had SH, 10,760 (30.4%) had DM; of these, 4166 patients (11.8%) developed AKI. Patients with AKI had higher admission and mean daily BG ($p < 0.001$), and had higher hospital mortality (3.5% vs. 0.5%, $p < 0.001$) compared to patients without AKI. In multivariate analyses adjusted for age, gender, and BMI,

severity of SH was independently associated with AKI: 140-180 mg/dl OR:1.05 (95% CI:0.93-1.18); 181-250 mg/dl OR:1.36 (95% CI:1.18-1.57); >250 mg/dl OR:1.53 (95% CI:1.24-1.89) compared to non-diabetic patients with BG<140 mg/dl. Also, in patients with AKI, severity of hyperglycemia was associated with increased mortality [181-250 mg/dL OR:1.41 (95% CI:1.06-1.87) , > 250 mg/dL OR:2.11 (95% CI:1.51-2.94)]. Patients with SH and AKI had higher total hospitalization costs (\$38,658, range: \$19,654–71,388) compared to DM patients with AKI (\$22,507, range:\$11,795–45,823, p<0.0001) and AKI with normoglycemia (\$20,461, range: \$11,331-41,872, p<0.0001). In summary, stress hyperglycemia and diabetes are associated with increased risk of AKI. Patients with stress hyperglycemia and AKI have higher inpatient mortality and hospitalization costs compared to diabetic and normoglycemic patients with AKI.

#37 (afternoon session)

Pendrin localizes to the adrenal medulla and modulates catecholamine release

Park AY, Pham TD, Beierwaltes WH, Sutliff RL, Verlander JW, Ellis CL, Wynne BM, Hoover RS, Wall SM, Lazo Fernandez Y

Pendrin (Slc26a4) is a Cl-/HCO₃- exchanger expressed in renal intercalated cells where it modulates blood pressure. Since pendrin gene ablation increases plasma renin, but not aldosterone, we hypothesized that pendrin is expressed in the adrenal gland and modulates adrenal cortical function. We examined rodent adrenal gland pendrin mRNA and protein abundance by PCR, immunoblot and immunohistochemistry. Pendrin was detected in epinephrine- and norepinephrine-producing chromaffin cells of the adrenal medulla rather than in adrenal cortical cells. The effect the pendrin gene ablation on adrenal medullary function was examined by measuring stress-induced catecholamine release. While basal levels of epinephrine (E) and norepinephrine (NE) were similar, E and NE levels were ~25-50% higher pendrin null than in wild type mice after 20 min of immobilization stress. 30 min following relief of stress, NE levels were 50% higher in pendrin null than in wild type mice. The mean arterial pressure (MAP), measured by telemetry, rose in both wild type and pendrin null mice following immobilization stress, but MAP in pendrin null mice was 16 mm Hg lower than in wild type mice under basal conditions and 12 mm Hg lower following 20 min of immobilization stress (P<0.05). However, 30 min after relief of stress, MAP was the same in both groups (Wild type 121± 1.33 versus 117 ± 3.5 mm Hg, pendrin null mice). We conclude that pendrin is expressed in mouse adrenal medulla where it plays a role in restraining catecholamine release during stress, which probably modulates pendrin-dependent changes in blood pressure.

#5 (afternoon session)

Comparison of clinical characteristics and hospital outcomes between type 1 and type 2 diabetes in the inpatient setting

Park P, Vellanki P, Fayfman M, Anzola I, Peralta G, Peng L, Pasquel F, Haw J, Smiley D, Umpierrez G

Few studies have focused on the clinical characteristics of hospitalized patients with type 1 diabetes (T1D). Using ICD-9 codes, we performed a retrospective study of 13,853 patients with T1D and T2D admitted to four university-affiliated hospitals during 2012-2013 to compare demographics, glycemic control, and clinical outcomes between T1D and T2D patients. Overall, 2.3% (n=312) patients had T1D compared to 97.7% with T2D (n=13,595). We analyzed the outcomes after 1:1 age-matching since patients with T1D were significantly younger than those with T2D (44±17 vs 61±19 years, p<0.001). In age-matched analysis, patients with T1D had lower BMI (26.2±5.9 vs 32.8±9.7, p<0.001) and higher percentage of multiple admissions (9% vs 4%, p=0.012). Admission glucose levels were higher (245±197 mg/dl vs 175±113 mg/dl, p<0.001) and hypoglycemic episodes more frequent (BG<70 mg/dl, 47% vs 18%, p<0.001 and <40 mg/dl, 18% vs 4%, p<0.001) in T1D compared to T2D. Patients with T1D also had increased prevalence of chronic kidney disease (36% vs 18%, p<0.001) and higher incidences of acute kidney injury (34% vs 19%, p<0.001) and lactic acidosis (15% vs 9%, p<0.001) compared to T2D. However, there were no differences in acute myocardial infarction, pneumonia, acute respiratory failure, and mortality between the two groups. Our data indicate significant differences exist in inpatient clinical characteristics between patients with T1D and T2D. Overall, patients with T1D have worse glycemic control and hospital complications than patients with T2D. Randomized controlled studies are needed to assess the impact of improved inpatient glycemic control on hospital outcomes in patients with T1D.

#14 (morning session)

Social determinants of health of veterans aging with HIV: a qualitative study

Perkins M, Halpin SN, Cooper H, Justice AC, Johnson II TM, McInnes DK, Ohl, M, Rentsch C, Carruth EC, Rimland D

Background: The "graying" of the U.S. HIV epidemic has become a major focus of the U.S. federal government's efforts to improve health outcomes of people living with HIV. Although a number of public health policy initiatives and research agendas emphasize the need to address social determinants of health (SDH) to improve health and reduce HIV-related disparities, a dearth of research focuses on SDH in context of older adults with HIV. Objectives: To identify SDH that impact health outcomes of veterans living and aging with HIV in Georgia.

Methods: We used maximum variation sampling to select 25 veterans from the Veterans Aging Cohort Study (VACS) at the Atlanta site who varied along dimensions salient to the study aims (e.g., age, race, income, sexual orientation, disease severity, functional status). Semi-structured interviews included

social network mapping and explored twelve broad domains germane to SDH and the experience of aging with HIV. We recorded and transcribed interviews verbatim and used interpretative phenomenological analysis to analyze the data.

Results: Veterans ranged in age from 50 to 75, with a mean age of 59. Most (80%) were male and African American (60%). We identified resilience and strength of weak ties (social ties that may seem inconsequential on the surface but matter) as major overarching themes. Challenges included caregiving difficulties (both as caregiver and care receiver), inadequate social support, and stigma and fear of disclosure.

Conclusions: Findings have implications for new policies and clinical practices that are better tailored to the needs of older persons with HIV.

#31 (afternoon session)

Palmitate induced endoplasmic reticulum stress is not mediated by Toll-like receptor 4 in cultured skeletal muscle
Perry BD, Rahner JA, Zheng B, Price SR

Chronically elevated circulating saturated fatty acids (SFA), as seen in Type 2 Diabetes Mellitus, impairs insulin sensitivity, protein synthesis, and upregulates proteolytic pathways in skeletal muscle. The SFA-induced impairment of muscle protein synthesis is due, in part, to increased endoplasmic reticulum (ER) stress and subsequent activation of the unfolded protein response. The upstream receptors that initiates ER stress in response to SFA in skeletal muscle are not well understood. Indirect evidence suggests the Toll-like receptor 4 (TLR4), that is activated by palmitate and initiates pro-inflammatory signaling, may induce ER stress. This study investigated whether TLR4 induces ER stress in cultured mouse muscle cells (C2C12). Cells were treated with either a vehicle, a TLR4-specific ligand (lipopolysaccharides; 100 ng/mL), palmitate (500 μ M), or a combination of a TLR4-specific inhibitor (TAK-242, 1 μ M) and palmitate. Cells were harvested after 24 hours treatment and analyzed for several mRNA markers of ER stress (ATF4, spliced XBP1 and CHOP) using qRT-PCR. As shown previously, palmitate treatment substantially increased mRNA levels of CHOP, spliced XBP1, and ATF 4. Unexpectedly, inhibition of TLR4 signaling did not prevent palmitate-induced ER stress and LPS did not increase any mRNA markers of ER stress. Intriguingly, the combination of palmitate and TAK-242 increased CHOP mRNA more than palmitate alone, and palmitate plus TAK-242 did not produce a qualitative improvement in myotube appearance compared to palmitate treatment. These data suggest that despite the pro-inflammatory effects of TLR4 activation in conditions involving lipotoxicity, SFA-induced ER stress in skeletal muscle is independent of TLR4 signaling.

#15 (morning session)

Association of referral for kidney transplantation with other indicators of quality care among incident Georgia dialysis patients: the RaDIANT community study
Plantinga LC, Patzer RE, Pastan SO

Background: Dialysis facility referral of patients for kidney transplant evaluation is a potential indicator of quality care, but it is unknown whether this referral is associated with other dialysis quality indicators among end-stage renal disease (ESRD) patients.

Methods: Using national registry data linked to referral data from Georgia kidney transplant centers, we identified 12,126 incident (7/05-9/11) adult (18-69 years) patients treated at 198 dialysis facilities. We obtained odds ratios for referral within 1 year of dialysis start with dichotomous quality indicators using multilevel, multivariable models.

Results: On average, facilities referred 25.0% of patients for transplant evaluation within 1 year of dialysis start. Patients with pre-ESRD nephrology care [OR=1.34 (95% CI, 1.21-1.48)], permanent vascular access in place [OR=1.54 (95% CI, 1.40-1.71)], and transplant information [OR=1.64 (1.44-1.87)] at dialysis start were more likely to be referred within 1 year. After dialysis start, higher waitlisting [OR=1.40 (95% CI, 1.18-1.68)] and transplantation [OR=1.25 (95% CI, 1.04-1.50)] at the facility were both associated with higher 1-year referral. The only non-transplant-related facility indicators associated with 1-year referral were lower levels of anemia [OR=1.24 (95% CI, 1.04-1.49)] and fewer transfusions [OR=1.33 (95% CI, 1.11-1.60)]; higher vaccination rates, better dialysis adequacy, and recommended dialysis access were not associated with referral.

Conclusion: In general, indicators related to quality of care before but not after dialysis start were associated with higher referral. Interventions to increase referral should target facilities with large proportions of patients lacking pre-ESRD care rather than facilities with low overall performance by standard dialysis quality metrics.

#18 (morning session)

Improving EMS recognition of severe sepsis: a survey study of emergency medicine faculty and EMS providers
Polito CC, Bloom I, Yancey A, Lairet J, Isakov A, Martin G, Sevransky JE

Background: Recognizing severe sepsis is a pivotal step in sepsis care. Emergency Medical Services (EMS) recognition is not currently standard of care. The purpose of this study was to assess perspectives regarding EMS recognition of severe sepsis.

Methods: Emergency Medicine faculty and Metro Atlanta EMS providers were surveyed using an online questionnaire. Seventy-five responses were obtained.

Results: Seventeen percent of EMS providers were unaware of evidence supporting early treatment of severe sepsis. In

addition, 20% of EMS providers disagreed that severe sepsis should be considered in the same category as other life-threatening, time-sensitive conditions including STEMI and stroke. Seventy-eight percent of faculty reported that sepsis, when present, is first suspected during initial evaluation in the ED; while 60% of EMS providers reported that sepsis, when present, is first suspected during the EMS phase of care. Regarding a theoretical EMS screening tool for severe sepsis, faculty was willing to accept a false negative rate of 10% and a false positive rate of 20%. Sixty-eight percent of faculty and 48% of EMS providers reported that an EMS screening tool would be useful if it expedited hospital admission. Faculty concerns about an EMS screening tool included the lack of coordinated care systems (37%), alert fatigue (28%), and EMS screening leading to unnecessary workup in the ED (19%).

Conclusions: Physicians prefer a highly sensitive and specific EMS screening tool for severe sepsis. Both physicians and EMS providers value a screening tool that expedites hospital admission. Future studies should incorporate this information to enhance buy-in.

#6 (afternoon session)

Hypoglycemia and outcomes in elderly patients with type 2 diabetes admitted to long-term care facilities

Powell W, Pasquel FJ, Smiley D, Doan J, Peng L, Vellanki P, Haw JS, Umpierrez GE

Treatment of geriatric patients with diabetes in long-term care (LTC) facilities is challenging due to increased risk of hypoglycemia. We randomized 150 LTC patients with type 2 diabetes and a blood glucose (BG) >180 mg/dL or HbA1c >7.5% to receive basal insulin (glargine) once daily or to continue oral antidiabetic agents (OAD) for 26 weeks. The primary outcomes were the difference in glycemic control as measured by fasting and mean daily BG. A total of 150 patients were randomized to basal insulin (n= 75) and OAD therapy (n= 75). There were no differences in mean fasting BG (131±27 mg/dL vs 123±23 mg/dL, p=0.06) between insulin and OAD groups, but patients treated with insulin had greater mean daily BG (163±39 mg/dL vs 138±27 mg/dL, p<0.001) compared to OAD group. There were no differences in the rate of hypoglycemia between insulin (27%) and OAD (31%) groups, p=0.58 or in a composite of hospital complications that included cardiovascular event, falls, infections, acute renal failure, emergency room visit, and hospital admission and death. Patients with hypoglycemia had longer length of stay (p=0.002) and higher rate of a composite of complications (40% vs 22%, p=0.033). The results of this randomized study indicate that elderly patients in long-term care facilities exhibit similar glycemic control, hypoglycemic events, and complications when treated with either basal insulin or with oral antidiabetic drugs. Treatment strategies aimed at preventing hypoglycemia and its complications are needed in this vulnerable population.

#32 (afternoon session)

C/EBP homologous protein modulates Liraglutide mediated attenuation of non-alcoholic steatohepatitis

Liu Y, Rahman K, Kumar P, Smith T, Thorn NE, Anania FA

Background and Aims: The CCAAT/enhancer-binding protein (C/EBP) homologous protein (CHOP) is implicated in lipotoxicity-induced hepatocyte apoptosis in non-alcoholic fatty liver disease (NAFLD). In the present study we investigated the role of CHOP in the mechanism of glucagon like peptide 1 (GLP-1) analog mediated restoration of endoplasmic reticulum (ER) homeostasis and hepatocyte apoptosis in a murine model of NAFLD.

Methods: C57BL/6 (WT) and CHOP deficient (CHOP^{-/-}) male mice were fed a high fat, high fructose and high cholesterol diet (HFCD) or normal diet (ND) for 16 weeks. After 12 weeks of feeding, saline or Liraglutide (GLP-1 analog) was administered daily for 4 weeks. At necropsy, liver tissue was subjected to histochemical, immunofluorescence, RNA, and protein analysis.

Results: Despite similar caloric intake, HFCD-fed CHOP^{-/-} mice developed more severe histological features of steatohepatitis compared with WT controls. Severity of steatohepatitis in HFCD-fed CHOP^{-/-} mice correlated with significant increase in ER stress mediated hepatocyte apoptosis. CHOP deficiency also resulted in the suppression of necroptosis evidenced by increased degradation of receptor-interacting protein 1 (RIP-1) and decreased expression of RIP-3 in HFCD-fed CHOP^{-/-} mice. Liraglutide treatment attenuated steatohepatitis in HFCD-fed WT mice by restoring ER homeostasis and reducing hepatocyte apoptosis. However, in the absence of CHOP, Liraglutide failed to attenuate ER stress and steatohepatitis.

Conclusions: Taken together, these data suggest that CHOP protects hepatocytes from HFCD-induced ER stress, and CHOP is required for Liraglutide mediated protection from NAFLD. Further, these data also implicate CHOP as a key player in protecting hepatocytes from HFCD-induced necroptosis.

#27 (afternoon session)

Overexpression of PGC1 α attenuates atrophy-related reduction in Akt phosphorylation

Rahnert JA, Perry BD, Zheng B, Price SR

Muscle wasting (atrophy) is a debilitating consequence of many conditions and has been linked to decreased expression of the transcriptional coactivator PGC-1 α . In some models of atrophy, including nutrient deprivation, overexpression of PGC-1 α has been shown to counter muscle loss, in part, by reducing FoxO-mediated atrophy gene expression. FoxOs are transcription factors that are regulated primarily by phosphorylation via Akt. Previous studies indicate that activation of Akt prevents downstream FoxO signaling during atrophy and that overexpression of PGC-1 α increases phosphorylation (i.e. inhibition) of FoxO. This study aimed to determine whether increasing PGC-1 α protein preserves Akt phosphorylation using an in vitro model of atrophy, starvation. C2C12 myotubes were

infected with an adenovirus encoding GFP (control) or PGC-1 α for 24h, followed by incubation in normal differentiation media (containing 2% horse serum in DMEM) or serum-free DMEM (SF) for the final 24h. Overexpression of PGC-1 α increased PGC-1 α protein and Akt phosphorylation compared to control. In GFP-expressing myotubes, incubation in SF reduced PGC-1 α protein and Akt phosphorylation by ~50%. Although the starvation-induced decrease in both PGC-1 α and phosphorylated Akt was greater in myotubes over-expressing PGC-1 α , the level of these proteins was not different from that of GFP-expressing control myotubes. While the mechanism by which starvation initially decreases PGC-1 α is unclear, these data suggest that raising PGC-1 α levels maintains Akt phosphorylation and supports the ability of PGC-1 α to preserve muscle protein content during atrophy.

#44 (morning session)

Risk Factors for Clostridium difficile infection recurrence
Reddy SC, Guh A, Lessa F, Mu Y, Beldavs ZG, Davis CM, Dumyati GK, Holzbauer SM, Johnston H, Lyons C, Phipps EC, Wilson LE, Winston LG, Gerding DN, McDonald LC, Farley MM

Background: In 2011 the US had approximately 83,000 Clostridium difficile infection (CDI) first recurrences. Identifying patients at risk of recurrent CDI (rCDI) can help tailor management and prevention.

Methods: Active laboratory- and population-based surveillance for CDI was conducted in 10 geographically-diverse US sites. Adult initial CDI cases (iCDI) were defined as the first positive C. difficile toxin or molecular assays on stool specimens from patients ≥ 18 years old with diarrhea or CDI treatment (metronidazole, vancomycin or fidaxomicin) during 2013 who did not have a previous positive specimen in ≥ 1 year; rCDI cases were the subset with a subsequent positive test and diarrhea or treatment 2-26 weeks after the first positive test. Demographics, clinical characteristics, and iCDI treatment were assessed for association with rCDI. Multivariable logistic regression modeling was used to estimate adjusted odds ratios (aOR) for rCDI.

Results: Of 4,790 iCDI cases, 42% were ≥ 65 years old, 63% community-associated, 63% treated with metronidazole, and 20% treated with ≥ 2 CDI antibiotics; 17% developed rCDI. In multivariable analysis, treatment with ≥ 2 CDI antibiotics (aOR 1.37 95%CI 1.12-1.68), white race (aOR 1.49, 95%CI 1.16-1.92), chronic renal insufficiency (aOR 1.41, 95%CI 1.10-1.79), diabetes mellitus (aOR 1.31, 95%CI 1.06-1.61) and antibiotic use in the 12 weeks prior to iCDI (aOR 1.50, 95%CI 1.21-1.85) increased the odds of rCDI.

Conclusions: Multiple factors for rCDI have been identified, including treatment with combination therapy. Additional study is warranted to develop a prediction tool identifying patients at high risk for rCDI.

#24 (afternoon session)

Shear stress regulation of the transcription factor ZBTB46 in endothelial cells and its role on endothelial cell activation
Sun HY, Kumar S, Kim CW, Jo H, Rezvan A

Background: ZBTB46 is a transcription factors, identified mostly as a transcription suppressor in classical dendritic cells, responsible for DC quiescence. Endothelial cells also express ZBTB46, although it's role in EC gene regulation is unknown. EC activation in areas exposed to disturbed flow is the initial step in atherosclerosis. We hypothesize that ZBTB46 expression is reduced in areas exposed to disturbed flow, leading to changes in gene expression and EC activation.

Methods: We used the mouse partial ligation model (in vivo), and a cone and plate model (in vitro), to examine ZBTB46 expression in response to disturbed flow. We used a ZBTB46 KO mouse, siRNA (downregulation) and AAV transfection (upregulation) to assess the role of ZBTB46 on EC gene expression. EC gene expression was assessed using gene arrays, qPCR and Western blot.

Results: ZBTB46 is expressed in both human and murine ECs, and is down-regulated by disturbed flow both in vivo and in vitro. ZBTB46 protein levels drop rapidly in response to disturbed flow, suggesting active degradation of the protein. ZBTB46 KO leads to significant gene expression changes in ECs. Pathway analysis suggests an anti-inflammatory role for ZBTB46 in ECs.

Conclusion: ZBTB46 is expressed in ECs, is regulated by shear stress, and contributes to EC quiescence. The rapid degradation of ZBTB46 in response to disturbed flow may be responsible for EC gene expression changes and a main mechanism for EC activation. Targeted manipulation of ZBTB46 expression may have therapeutic potential in conditions such as atherosclerosis or organ transplants.

#44 (afternoon session)

Novel polymer based strategy for delivery of mesenchymal stem cells for cardiac regeneration
Saraf A, Headen D, Weiss D, Joseph G, Brown M, Davis ME, Garcia A, Taylor WR

Approximately 1.2 million Americans suffer from heart attacks each year. Following myocardial injury, 1 in 3 will develop congestive heart failure within 5 years as a result of compromised cardiac function. The delivery of mesenchymal stem cells (MSCs) to regenerate damaged heart tissue is a new frontier in cardiovascular therapy. MSCs are an ideal candidate for therapy as they secrete beneficial paracrine factors that recruit progenitor cells, promote angiogenesis, and limit inflammation and formation of scar tissue. These current limitations of MSC therapy may be largely attributable to poor distribution of these cells across areas of ischemia as well as their inability to be retained within the cardiac tissue after delivery. Our strategy facilitates a uniform distribution of encapsulated MSCs to the cardiac tissue and increases retention of the encapsulated MSCs by capturing them within terminal

capillaries of the heart. MSCs encapsulated in poly-ethylene glycol microparticles (MPs) were optimized using microfluidics technology. MPs had a mean diameter of 25.3 μm without cells and 43.7 μm with cells. After perfusion, the MPs uniformly distributed along the myocardium as demonstrated by fluorescence imaging. Contractility of the heart was tested using an ex-vivo isolated heart perfusion model (Langendorff) and systolic function was found to be preserved when 100k MPs were perfused retrograde through the aorta. Histological frozen sections showed localization of MPs in terminal vessels of the heart.

#42 (morning session)

Prevalence of chlorhexidine resistance in methicillin resistant *Staphylococcus aureus* and association with the *qac* genes

White T, Satola SW

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important pathogen that causes a number of infections from skin and soft tissue infections to potentially life-threatening infections such as osteomyelitis, bloodstream infections and pneumonia. MRSA is usually spread by direct contact with an infected wound, by contaminated hands or via asymptomatic carriers. Surface-active antiseptics, such as chlorhexidine, are increasingly used to prevent MRSA transmission within the hospital by decontaminating surfaces, surgical equipment, as well as decolonizing patients, risking potential for increased resistance. The *qac* genes encoding efflux pumps have been found in MRSA that are highly resistant to chlorhexidine. We examined the chlorhexidine susceptibilities and distribution of antiseptic-resistance genes (*qacA/B*) in 216 MRSA invasive isolates collected in 2013, as part of the Georgia Emerging Infections Program. Broth Microdilution was conducted to determine the minimum inhibitory concentration (MIC) to chlorhexidine and PCR was used to identify isolates with the *qacA/B* gene. We found 1/216 (0.5%) of the isolates carried the *qacA/B* gene, 162/216 (75%) isolates had MICs susceptible to chlorhexidine ($\text{MIC} \leq 4 \mu\text{g/mL}$), 50/216 (23.1%) had MICs with increased or intermediate resistance to chlorhexidine ($\text{MIC}=8\text{-}16 \mu\text{g/mL}$) and 4/216 (1.9%) showed high level resistance ($\text{MIC} \geq 32 \mu\text{g/mL}$). Out of 216 isolates, 0.5% tested positive for the *qacA/B* gene but a significant number of the isolates had an increased tolerance to chlorhexidine. We can conclude that resistance to chlorhexidine may be a larger problem than previously thought and not always associated with the presence of the *qacA/B* gene.

#1 (afternoon session)

Mycobacteriology diagnostic costs in an inner-city public hospital: are we ready to adopt the Xpert[®] MTB/RIF in lieu of the Acid-Fast Bacilli (AFB) Smear?

Schechter MC, Snoeyenbos G, Wang YF, Holland DP, Ray SM

Background: Grady Memorial Hospital is a 650-bed urban safety-net hospital in a high tuberculosis (TB) incidence area. Our current mycobacterial diagnostic practice involves AFB smear and culture (cx) for all samples. Xpert[®] is automatically performed on smear positive samples ("selective Xpert"

algorithm"). We sought to compare our current algorithm with (a) "universal Xpert, no smear" approach in which all samples are submitted for culture and only 1 sample per patient is tested with Xpert[®] (b) "universal Xpert with smear" algorithm in which, all samples are processed for culture and smear and only 1 sample per patient is tested with Xpert[®].

Methods: Lab records for patients with respiratory specimens submitted for smear and cx from October 1 to December 31, 2014 were reviewed. Estimated costs (in US\$) of smear, cx, and Xpert were based on published cost analyses. Patients diagnosed by Xpert were defined as "early TB diagnosis"; patients diagnosed by culture only were defined as "delayed TB diagnosis".

Results: 319 patients submitted 650 specimens (2.03 per patient). 10 patients were diagnosed with TB; 7 had a positive smear. Both universal Xpert approaches, with or without smear, would avert 2 delayed TB diagnoses; a 66.6% reduction compared to the "selective Xpert" algorithm. A low cost Xpert could make algorithms that do not involve smears attractive from a laboratory cost perspective.

Conclusion: The addition of universal Xpert to our current algorithm would reduce delays in TB diagnosis, which may have significant benefit to both individual and public health.

#43 (morning session)

Macrolide-resistance mechanisms in invasive *Streptococcus pneumoniae* in Atlanta, Georgia, following introduction of pneumococcal conjugate vaccines, a 20 year study

Schroeder MR, Thomas SM, Chancey ST, Farley MM, Stephens DS

We assessed the major mechanisms of macrolide-resistant in *Streptococcus pneumoniae*, ribosomal methylation encoded by *erm(B)* and macrolide efflux encoded by *mef(E)/mel*, following the introductions of pneumococcal conjugate vaccines (PCV)-7 in 2000 and PCV-13 in 2010. Using prospective population-based surveillance in Atlanta, Georgia from 1994-2013, the incidence of macrolide-resistant invasive pneumococcal disease (IPD) decreased 55.9% 2000-2004 (9.3 per 100,000 in 1999 to 4.1 per 100,000 in 2003) and decreased again following PCV-13 introduction in 2010 (3.7 per 100,000 in 2009 to 2.4 per 100,000 in 2013). During the PCV-7 era (2000-2010), macrolide resistant IPD stabilized around 4.0 per 100,000. During this time, macrolide resistant serotype PCV-7 serotypes continued to decrease while non-PCV-7 macrolide resistant serotypes increased (most notably 19A and 15A). The incidence of *mef(E)/mel* steadily decreased after introduction of PCV-7 (7.7 per 100,000 in 1999 to 3.5 per 100,000 in 2003) and remained constant after the introduction of PCV-13 (1.4 per 100,000 in 2009 and 1.3 per 100,000 in 2013), while *erm(B)* decreased initially after PCV-7 introduction but has modestly increased since 2003 (0.22 per 100,000 to 0.63 per 100,000 in 2013). Macrolide resistance caused by a 19A strain containing both resistance determinants, *mef(E)/mel* and *erm(B)*, was first observed in 1999 (0.04 per 100,000) and expanded throughout

the PCV-7 era peaking in 2010 (1.38 per 100,000). Following PCV-13 introduction, a 74.6% decrease in *me(E)/mel* and *erm(B)* dual resistant strains occurred (0.35 per 100,000 in 2013). The incidence of macrolide-resistant IPD in Atlanta declined 74% after PCV-7 and PCV-13 introduction.

#10 (afternoon session)

Assessment of factors that predict postoperative prophylaxis use in patients who undergo Crohn's-related surgeries

Shea L, Iskandar H, Clermont M, Srinivasan J, Dhare T

Despite medical therapies, up to 70% of Crohn's disease (CD) patients will require surgery in their lifetime. Over 75% of these patients will develop evidence of endoscopic recurrence which can be prevented with the use of post-operative prophylaxis with immunosuppressives. We studied a group of patients who underwent CD related surgeries to identify factors including race that may predict being placed on post-operative prophylaxis. With Institutional Review Board approval, the medical records of our institution were queried to identify patients who underwent surgery for CD from December 1, 2009 to December 1, 2011. A retrospective chart review was performed. Statistical analysis included descriptive statistics, Chi-square analysis for categorical variables, and a logistic regression model. A total of 77 patients were included in the study. Of these 69 patients (89.6%) were felt to be appropriate for postoperative prophylaxis. Table 1 highlights the proportion of eligible patients started on immunosuppressives and who followed up with a gastroenterologist within 3 months postoperatively based on ethnicity. In a logistic regression model (table 2), adjusting for age, ethnicity, and prior CD surgery, the only significant predictor of starting post-operative therapy was seeing a gastroenterologist within 3 months (OR 6.5, 95% CI 1.6-26, p=0.008). When comparing multiple factors including ethnicity, prior CD surgery, age, and GI physician follow up, the only significant predictor of starting post-operative immunosuppressive therapy was follow up with a gastroenterologist. Institution of measures to assure follow up may help to prevent further complications of CD in those who undergo surgery.

#45 (morning session)

The relationship between persistent low-level viremia and antiretroviral concentrations in hair among HIV-infected women on antiretroviral therapy in the United States

Aguirre AJ, Mehta CC, Ofotokun I, Hussen SA, Greenblatt RM, Merenstein D, Kashuba AD, Anastos K, Kempf MC, Golub ET, Dehovitz JA, Milam J, Cohen MH, Sheth AN

Background: Many HIV-infected patients on combination antiretroviral therapy (cART) experience episodes of low-level viremia (LLV). Persistent LLV is associated with antiretroviral (ARV) drug resistance and regimen failure, but its etiology is not known. We investigated virologic outcomes in a cohort of HIV-infected women receiving cART and evaluated the relationship between persistent LLV and the concentration of ARVs in hair, a measure of long-term ARV exposure.

Methods: HIV-infected women enrolled in the Women's Interagency HIV Study who reported cART for ≥ 1 year and plasma viral load (VL) < 500 copies/mL were followed until VL > 500 copies/mL (virologic failure), cART discontinuation, or end of study, and classified by virologic outcome. Women with persistent LLV (≥ 2 consecutive detectable VL < 500 copies/ml) were compared to those with sustained virologic suppression using multivariable logistic regression models.

Results: Among 1314 participants, virologic suppression, intermittent LLV, persistent LLV and virologic failure occurred in 33%, 24%, 12% and 31%, respectively. In multivariable analysis, receipt of ritonavir-boosted protease inhibitors was significantly associated with persistent LLV (OR 2.28, 95%CI 1.11–4.66). In multivariable analysis including the subset of women with hair ARV concentrations, hair ARV concentrations in the lowest quartile was associated with persistent LLV compared to the highest quartile (OR 2.75, 95%CI 1.40–5.40).

Conclusions: In this large cohort of HIV-infected women, more than one-third experienced either persistent LLV or virologic failure. Persistent LLV was more likely to occur among women with the lowest ARV exposure, suggesting that improving ARV exposure could prevent persistent LLV and its adverse consequences.

#45 (afternoon session)

Encapsulated mesenchymal stem cells improve cardiac strain following myocardial ischemia reperfusion injury

Shin EY, Levit R, Taylor WR, Zemskova M

Background: Cardiac ischemia reperfusion (IR) following acute myocardial infarction remains an unaddressed pathologic mechanism that predisposes patients to cardiomyopathy. Effective strategies for cardio-protection following revascularization are currently lacking. Cell based therapy may serve as a critical tool to improve hemodynamic function by modulating the early immune response in IR injury.

Methods: Adult rats underwent ligation of the left anterior descending artery for 30 minutes. Prior to reperfusion, rats were grouped into either those receiving no treatment or those receiving hydrogel encapsulated mesenchymal stem cells (MSCs) implanted on the anterior wall of the myocardium. Transthoracic echocardiography was performed prior to surgery and at days 1, 2, and 7 post-operatively. Left ventricle dimensions, fractional shortening, ejection fraction, global longitudinal strain (GLS), and global longitudinal strain rate (GLSR) were assessed.

Results: GLS and GLSR were significantly reduced in both groups immediately following IR injury at days 1 and 2 with no difference being observed between rats subjected to IR only versus IR with encapsulated MSCs. At 7 days, rat hearts treated with encapsulated MSCs demonstrated improvement compared to IR injured only rats in terms of both GLS (20.6% vs. 11.7%, $p < 0.05$) and GLSR (4.04s⁻¹ vs 2.70s⁻¹, $p < 0.05$). Use of encapsulated MSCs did not affect the rate operative mortality.

Conclusion: Encapsulated MSCs are safe and viable in improving hemodynamic function in a rat model of IR injury. Although mechanisms have not been elucidated, paracrine factors secreted from implanted MSCs may attenuate the action of critical mediators in the inflammatory response following reperfusion.

#14 (afternoon session)

A randomized, double-blind controlled trial to examine the effectiveness of lubiprostone on constipation symptoms and colon transit time in diabetic patients

Shroff S, Shahnavaz N, Carter L, Harrison M, Dietz-Lindo K, Hanfelt J, Srinivasan S, Christie J

Introduction: Constipation is the most common GI symptom in patients with diabetes mellitus (DM). Patients with constipation have lower health-related quality of life than those without constipation and effective therapies for constipation are limited.

Methods: Diabetic patients with chronic idiopathic constipation (CIC) were recruited from a tertiary care center and a Veterans Administration Hospital. Baseline demographics, stool patterns, associated GI symptoms, quality of life, and colonic transit time (CTT) were evaluated. Patients were randomized in a double-blind fashion to lubiprostone or placebo for 8 weeks. The primary endpoint measured was the difference in number of spontaneous bowel movements (SBMs) per week vs. baseline for each group at 2, 4, and 8 weeks after initiation of therapy. Secondary endpoints included changes in stool patterns, associated GI symptoms, quality of life, and CTT.

Results: 76 patients (mean age 56.8±8.9 years, 65.8% Females) were enrolled and 62 patients completed the study. During the 8-week treatment period, patients in the lubiprostone group experienced an average of 2.15±0.86 (p=0.01) more SBMs per week than those in the placebo group as compared with baseline. The lubiprostone group experienced a significantly greater decrease in average CTT at week 4 than the placebo group (-6.59±30.17 vs. 11.14±23.88 hours, p=0.04) when compared to baseline. There was no significant difference in quality of life and associated GI symptoms between the two groups after 8 weeks.

Discussion: This study suggests lubiprostone is a safe and effective treatment for increasing weekly SBMs and decreasing CTT in patients with DM and CIC.

#35 (morning session)

Modulation of the dendritic cell-T cell axis by Mycobacterium tuberculosis

Sia JK, Madan-Lala R, Rengarajan J

CD4 T cells are critical for immunity against Mycobacterium tuberculosis (Mtb), but antigen specific, interferon gamma (IFN- γ)-producing TH1 responses are delayed and insufficient for bacterial clearance. Further, it is increasingly appreciated that additional T cell subsets, such as TH17 cells, play an important

role in the host response to tuberculosis (TB) but the early events that lead to TH1 and TH17 responses in TB remain unclear. Priming and polarization of naïve T cells are dependent on dendritic cells (DCs), but how Mtb influences DC-T cell interactions remains poorly understood. We hypothesized that Mtb infected DCs are impaired at activating costimulatory pathways and prevented from optimal priming and polarization of antigen specific CD4 T cells. We previously showed that wild type Mtb impairs DC functions, including maturation, cytokine production and antigen presentation. We now show that Mtb inhibits CD40 expression on infected DCs and engagement of CD40 significantly improves DC maturation and cytokine production. Cross-linking CD40 on Mtb-infected DCs enhanced the induction of IL-17 responses from antigen specific CD4 T cells to Mtb in vitro, suggesting that activation of the CD40 pathway in DCs is sufficient for induction of TH17 in the context of Mtb infection. We conclude that Mtb does not optimally activate DCs, resulting in poor induction of potentially protective TH17 responses. Furthermore, we identify CD40 engagement on DCs as a potential avenue for improving the IL-17 response during Mtb infection. Studies are underway to understand the role of TH17 and CD40 in protective immunity against Mtb in vivo.

#54 (morning session)

Vitamin D reduces hepcidin concentrations independent of inflammatory cytokines in healthy adults

Smith EM, Kearns MD, Alvarez JA, Zughaier SM, Tangpricha V

Objective: Disturbances in iron recycling may result from elevations in inflammatory cytokines and hepcidin, the major iron-regulatory hormone. Vitamin D is associated with reduced odds of anemia of inflammation, though its effect on iron recycling in healthy individuals is unclear. Our objective was to 1) examine the effect of high-dose vitamin D on hepcidin and inflammatory cytokine concentrations in healthy adults, and 2) determine whether changes in hepcidin were concomitant with or independent of changes in cytokines.

Methods: This was a double-blind, placebo-controlled trial in healthy adults (n=28) randomized to receive an oral dose of 250,000 IU D3 or placebo. Between- and within-group differences in plasma hepcidin and inflammatory cytokine [interleukin (IL)-1 β , IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1)] concentrations at baseline and 1 week were determined using two-sample and paired t-tests, respectively.

Results: At baseline, 25-hydroxyvitamin D [25(OH)D], hepcidin, and inflammatory cytokine concentrations did not differ between groups; 75% of subjects had plasma 25(OH)D concentrations < 20 ng/mL. By 1 week, those who received vitamin D3 experienced a 73% reduction in plasma hepcidin (geometric mean ratio: 0.27, P=0.005) compared to no change with placebo (P=0.11). Cytokines did not change significantly in either group.

Conclusion: High-dose vitamin D significantly reduced plasma hepcidin concentrations in healthy adults 1 week post-dosing; no change was observed in inflammatory cytokines. These findings suggest that in the absence of inflammatory conditions, vitamin

D may have a role in regulating iron recycling by acting directly on hepcidin, independent of changes in inflammatory markers.

#55 (morning session)

Macrophages from HIV transgenic rats demonstrate abnormal but reversible macrophage polarization

Staitieh BS, Fan X, Neveu W, Guidot DM

Macrophage phenotype and function is highly dependent on the signals present in their environment. A spectrum of different polarization states exist: at one pole is the M1 macrophage, an effector cell of the innate immune system, and at the other is the M2 macrophage, which is associated with wound-healing processes. Certain diseases such as HIV infection polarize the macrophage population toward an M2 state, likely contributing to the increased risks of infection and pulmonary fibrosis seen in that patient population. We performed a series of experiments to determine the plasticity and functional implications of the skewed macrophage population in an HIV transgenic rat model. At baseline, the macrophages were predominately in the M2 state, as expected. In response to bleomycin, a fibrotic insult, the cells were pushed even further toward the M2 state than wild-type macrophages and also produced more pro-fibrotic TGF- β 1. In response to GM-CSF, a key cytokine for the M1 state, macrophages demonstrated significantly improved phagocytic function and restoration of wild type macrophage polarization. These experiments demonstrate that macrophages from HIV transgenic rats demonstrate higher levels of M2 markers than macrophages from wild type rats even in the presence of a fibrotic insult. Treatment with GM-CSF restores both phagocytic function and wild type polarization, suggesting that the abnormal polarization caused by HIV can be reversed. Further experiments are necessary to better delineate the consequences of abnormal M2 polarization for the host and to determine the viability of GM-CSF as a potential therapeutic.

#8 (morning session)

Expansion of EQUIPPED: two-site results from an initiative to improve prescribing practices in the emergency department

Stevens MB, Vandenberg A, Schmidt AJ, Ikpe-Ugbo I, Clevenger C, Johnson TM, Vaughan CP

EQUIPPED is a multi-component, interdisciplinary QI initiative in eight VA EDs. Results for trained staff at the first site have been described previously. This abstract describes results for all providers (trained and untrained) at the first and second implementation sites. Methods: EQUIPPED aims to decrease the use of PIMs prescribed to Veterans aged 65 years and older at the time of ED discharge. Interventions include: 1) provider education; 2) clinical decision support with EMR embedded geriatric pharmacy order sets and links to online geriatric content; and 3) individual provider academic detailing, audit and feedback, and peer benchmarking. Trained staff at both sites received all interventions. Untrained/moonlighting providers at both sites had access to clinical decision support tools only. Data were examined from April 2012 to Nov 2014. Poisson regression was used to compare the number of PIMs at both sites before

and after EQUIPPED. RESULTS: At the first site trained providers prescribed 43% of all meds compared to 57% by untrained providers. At the second site trained providers prescribed 34%, and untrained 66%. The average monthly proportion of PIMs prescribed by all providers at the first site was 11.8% (SD 1.8) pre-intervention compared to 6.3% (SD 2.0) post intervention ($p < 0.0001$); and 8.0% (SD 0.9) compared to 7.0% (SD 1.8) $p < 0.006$ at the second site. Conclusions: EQUIPPED led to a significant and sustained reduction of PIMs prescribed to older Veterans at the first two implementation sites and suggests the program impacted all ED providers including those who did not receive all interventions.

#51 (morning session)

Specific detection of bacterial infection associated with cardiac electronic implantable devices: towards the clinical application

Takemiya K, Wang X, Seo W, Ning X, Mohammad R, Joseph G, Titterington JS, Weiss D, Kraft CS, Murthy N, Goodman M, Taylor WR

Background: Bacterial infection is a serious complication of implantable cardiac electronic devices, and the early detection has been a clinical challenge. To achieve this goal, we developed a new maltohexaose based near infra-red fluorescent imaging probe, maltohexaose-ICG (MH-ICG), and evaluated this new probe in terms of safety and utility for the early stage detection of bacterial infections of cardiac devices in a rat model.

Methods and results: To evaluate the cytotoxicity of MH-ICG, CHO-K1 cells and human umbilical vein endothelial cells were cultured with MH-ICG for 72 hours. Using a cell viability assay based on cell metabolism, MH-ICG showed no toxicity in these cell lines up to 20 μ M. To evaluate whether MH-ICG would accumulate in the infected area, Sprague-Dawley rats were implanted with stainless steel device mock-ups and were injected with 1×10^9 CFU/0.1 ml *Staphylococcus aureus* around the mock-ups on post-operative day 4. On post-operative day 6, the rats were injected with 0.25ml of 1mM MH-ICG, and scanned with an in vivo fluorescent imaging device. In the device infection group, the fluorescent signal around the mock-up area was two times higher than that in the control group at 6 hours after the injection of MH-ICG, and the accumulation was observed up to 24 hours after the injection.

Conclusion: With low toxicity to mammalian cell lines, MH-ICG detected bacterial device infection sensitively and specifically in a rat model, indicating the potential utility of this imaging agent in detecting bacterial infections in man.

#42 (afternoon session)

Thyroid hormone mediated mitogenic signaling in cardiomyocytes requires H₂O₂

Tan L, Torres RA, Caesar C, Husain A, Naqvi N

Thyroid hormone (T3)-mediated cardiomyocyte replication increases the cardiomyocyte population during preadolescence (Naqvi et al., Cell 2014). Here, we study the molecular

mechanism of T3-mediated activation of the cell cycle in early postnatal cardiomyocytes *in vitro*. Under serum free conditions, T3 increased the expression of cyclin D1 and cyclin B1, which are required for cell cycle and mitosis entry, respectively. This increase in cell cycle protein expression was indirect; it was due to increased expression of insulin-like growth factor-1 (IGF-1). T3-dependent IGF-1 expression results in activation of proliferative signaling molecules p44/42-Erk MAPK through phosphorylation at Thr202/Tyr204. Surprisingly, T3-mediated induction of IGF-1 was also indirect. We show that T3 increases hydrogen peroxide (H₂O₂) generation through a generalized increase in mitochondrial biogenesis. Furthermore, this effect on IGF-1 expression was caused by very low concentrations (0.5–15 μM) of H₂O₂. T3-dependent IGF-1 production was completely inhibited by blocking mitochondrial biogenesis through NRF1 inhibition, or by quenching H₂O₂ using PEG-catalase. Inhibition of IGF-1 using a neutralizing antibody also inhibited T3-dependent increases in pErk and cyclin D1, without inhibiting H₂O₂ generation, and an Erk inhibitor inhibited T3-mediated increase in cyclin D1. Collectively, this indicates that H₂O₂ signaling is upstream of IGF-1 as well as pErk/cell cycle activation by T3. Finally, *in vivo* blockade of H₂O₂ generation repressed the preadolescent increase in the cardiomyocyte population. We conclude that T3 functions as a cardiomyocyte mitogen in early postnatal cardiomyocytes through H₂O₂/IGF-1/IGF-1R/pErk signaling.

#51 (afternoon session)

MicroRNA detection using a double molecular beacon approach: distinguishing between miRNA and pre-miRNA *In vitro* and *in vivo*

James AM, Thomas SA, Baker MB, Bao G, Searles CD

MicroRNAs (miRNAs) are small, noncoding RNAs that post-transcriptionally regulate gene expression and are recognized for their roles both as modulators of disease progression and as biomarkers of disease activity, including neurological diseases, cancer, and cardiovascular disease (CVD). Commonly, miRNA abundance is assessed using quantitative real-time PCR (qRT-PCR), however, qRT-PCR can be labor intensive, time consuming and may lack specificity for detection of mature versus precursor forms of miRNA. Molecular beacons, however, have shown to be both highly specific and easy to use. Here, we describe a double molecular beacon approach that can distinguish and quantify mature versus precursor forms of miR-21 and-27b in a single assay, which is essential for use of miRNAs as biomarkers for disease. Using this approach, we found that molecular beacons with DNA and combined locked nucleic acid (LNA)-DNA backbones can detect mature and precursor miRNAs (pre-miRNAs) at low (< 1 nM) abundance *in vitro*. Compared to qRT-PCR and the single molecular beacon assay, the double molecular beacon assay was the most accurate in assessing miRNA abundance. In contrast, qRT-PCR and the single molecular beacon assay overestimated miRNA abundance. Additionally, the double molecular beacon assay was less labor intensive than traditional qRT-PCR and had 10-25% increased specificity. Our data suggest that the double molecular beacon-based approach is more precise and specific than previous methods, and has the promise for being the

standard for assessing miRNA levels in biological samples to establish clinical relevant miRNA biomarkers for CVD.

#56 (morning session)

Hepatic insulin gene therapy inhibits liver and intra-abdominal fat accumulation in diabetic mice

Thule PM, Jia D, Olson DE, Zhang J, Zhao Y

Diabetes mellitus and obesity are risk factors for non-alcoholic fatty liver disease (NAFLD). Recent data that increased liver glycogen contributes to hepatic steatosis, and may inhibit peripheral lipolysis suggest that hepatic glycogen content serves as a sensor for energy homeostasis (Nature Comm 4:2316, 2013, Diabetes 63, 2935, 2014). We have established hepatic insulin gene therapy (HIGT) as a treatment for diabetes mellitus in rodents. Liver expression of insulin from a metabolically responsive promoter produces near normal random blood sugars, and normalizes growth of STZ treated animals. Unexpectedly, HIGT reduces both hepatic glycogen and triglyceride content. We posited that reduced hepatic glycogen and triglycerides in HIGT mice may lead to reduced intra-abdominal fat accumulation. Two series of STZ-diabetic mice were treated with HIGT. In the first, liver glycogen, triglycerides, and genes important for lipid synthesis, oxidation, and secretion were assessed by RT-PCR. In the second, liver glycogen, triglycerides, and epididymal fat pad weights were assessed. HIGT reduced blood sugars to normal in fed DM mice, yet reduced liver glycogen and triglyceride content to less than normal ($p < 0.05$) in both series. Expression of genes responsible for lipid synthesis (SREBP1c, LxR α , FAS, ACS1) or lipid oxidation (PGC1a, CPT-1, PPAR α , ACADM) were not different in HIGT vs Con mice. However, HIGT mice exhibited diminished epididymal fat pad weights (Con 0.64 ± 0.07 vs HIGT 0.50 ± 0.07 mg/g bw, $p < 0.05$). We conclude that liver glycogen depletion in fed STZ-mice with normal blood sugars, inhibits intra-abdominal fat deposition.

#30 (morning session)

Deep sequencing of acute lupus nephritis kidney tissue identifies target B cell populations in the periphery

Tipton CM, Hong SH, Fucile CF, Chida AS, Hom J, Wei C, Rosenberg A, Sanz I

Acute systemic lupus erythematosus (SLE) flares progress with antibody-secreting cell (ASC) population surges resulting from a combination of traditional memory recall responses and a massive generalized activation of naive B cells. The striking contribution of these recently activated naive B cells (acN) is largely seen in next generation sequencing (NGS) data of immunoglobulin heavy chain transcripts, showing a highly polyclonal repertoire accentuated by a large number of sequences with low somatic mutation frequency. Clonal relatedness points to high levels of congruence between ASC and acN populations, which also display elevated cell numbers in SLE patients. However, it is unknown how this recruitment of acN cells and subsequent increase in ASC numbers play a role in patients experiencing flares of acute lupus nephritis, a severe condition that often results in kidney failure. Using multi-color

flow cytometry of kidney tissue biopsies from lupus nephritis patients, we demonstrate that the cells often share a similar phenotype to acN and IgD-CD27- (DN) cells from the periphery. Using NGS and single cell monoclonal antibody production, we determined that the cells produce autoreactive, highly selected antibodies and are clonally related to ASC, DN and acN from the peripheral blood. Substantial clonal expansions were found in the kidney tissue, many of which mirror the expanded clones identified in the periphery. Elucidating the origin and antigenic reactivity of pathogenic clones will improve our understanding of disease pathogenesis, enhance our ability to predict the development of nephritis and improve treatment through individualized B cell therapies.

#31 (morning session)

Analysis of SLE plasmablasts by high throughput pairing of the immunoglobulin heavy and light chain (VH-VL)

Tomar D, Tipton CM, Sanz I

In-depth analysis of the molecular and antigenic properties of antibody secreting cells (ASC) is critical for our understanding of autoimmune diseases. This goal however has been hampered by technological barriers imposed by low-throughput technologies to interrogate the ASC at the single cell level. We describe here the incorporation of a high throughput methodology for linking the B cell receptor's heavy and light chain variable region (VH and VL) for analyzing the plasmablast B cell population from a SLE patient. Conventional techniques for sequencing of genomic DNA or cDNA from single cells are limited by low efficiency and low cell throughput (<200–500 cells), whereas >2 x 10⁶ B cells per experiment can be analyzed by this single-cell, emulsion-based technology for sequencing antibody VH-VL repertoires. We use a flow focusing apparatus to encapsulate the single B cells in to the emulsion droplets containing the lysis buffer and oligo dT magnetic beads for capturing the mRNA, followed by an emulsion RT-PCR for generating the VH and VL linked products for next generation sequencing. Approximately 50,000 plasmablasts (CD19+IgD-CD27^{high}CD38^{high}CD138^{neg}) from a SLE patient were flow sorted and VH and VL transcript were linked using emulsion RT-PCR. 20,000 different sequences representing over 2,200 different clonotypes were identified, thereby demonstrating a very polyclonal PB repertoire during Lupus flares. High concordance was shown with Illumina miseq data obtained from bulk PB obtained from a separate aliquot of the same blood draw. Both experiments also demonstrated the presence of substantial clonal expansions of the SLE-associated VH4-34 clones. The ability of this approach to combine deep sequencing with single cell antibody generation should greatly enhance our understanding of the antigenic triggers involved in the pathogenesis of SLE and other autoimmune diseases.

#43 (afternoon session)

Myocardial cell rescue by ROS-dependent activation of intrinsic IGF-1 signaling in ischemia injured hearts

Torres RA, Tan L, Tejada T, Naqvi N, Husain A

It is widely believed that cardiomyocyte death occurs within minutes to a couple of hours after the blood supply to the ischemic myocardium is restored. Thus cardioprotective therapy is given only at, or a few minutes after, the start of reperfusion and is discontinued after a few hours. Contrary to existing dogma, we show that a meaningful number of cardiomyocytes in the ischemia injured heart die days after the start of reperfusion. Using an unbiased transcriptome analysis between uninjured mouse hearts versus those subjected to 90 minutes of ischemia and then reperfusion (I/R) for 72 h, we found a marked upregulation of several proapoptotic genes in 72 h post-I/R hearts. Surprisingly, gene expression studies also revealed prominent upregulation of the pro-survival factor IGF-1. Using a pharmacologic approach we show that this delayed induction of intrinsic IGF-1 signaling inhibits myocardial apoptosis and cardiac injury days after reperfusion. We further show that the delayed increase in cardiac IGF-1 mRNA post-I/R injury is reactive oxygen species (ROS) dependent. Administration of ROS scavenger (N-acetylcysteine, 3 mg/kg/day) from 24–72 h after I/R significantly decreased IGF-1 mRNA levels compared to vehicle treated mice. Collectively, our studies identify a novel window of opportunity for "late myocardial cell rescue" with potential therapeutic implications for patients with ischemic injury. Furthermore, these studies suggest caution in the timing for the use of anti-oxidant therapies post-ischemic injury.

#36 (afternoon session)

Polymerase delta interacting protein 2 controls mitochondrial dynamics and energy production, affecting cell cycle regulation in vascular smooth muscle cells

Torres G, Seidel-Rogol B, Benavides G, Darley-Usmar V, San Martin A

Mitochondrial dynamics impact cell metabolism and proliferation. The polymerase delta interacting protein 2 (Poldip2), which regulates cell cycle progression, localizes to mitochondria. We hypothesize that Poldip2 controls proliferation through the regulation of mitochondrial dynamics and bioenergetics in VSMCs. Using confocal microscopy, we found that Poldip2 downregulation increases mitochondrial volume and decreases mitochondrial number, consistent with a hyper-fused phenotype. Importantly, this phenotype was accompanied by a repression in ATP production, evaluated by Seahorse, and diminished cell proliferative capacity. The AMP-activated protein kinase phosphorylates p53 inhibiting cell cycle. Therefore, we sought to investigate if the AMPK/p53/p21 pathway was responsible for the Poldip2-mediated regulation of VSMC proliferation. We found that p53 was phosphorylated at Ser15 (consensus site for AMPK) in Poldip2 deficient cells while the expression of p21 was significantly activated. Altogether, our work shows that Poldip2 controls VSMC proliferation by regulating mitochondrial dynamics and bioenergetics.

#33 (afternoon session)

Redox-dependent regulation of Guanine Nucleotide Dissociation Inhibitor and GTPase activity during cell migration

Valdivia A, Duran C, San Martin A

Vascular smooth muscle cells (VSMCs) migration, which participates in vascular diseases, is controlled by Nox1-dependent mechanisms. The activity of the small GTPases Rho, Rac and Cdc42 is required for the cytoskeleton dynamics that supports cell migration. GTPase activity is regulated in part by the Guanine Nucleotide Dissociation Inhibitor (GDI) which keeps GTPases in the cytoplasm protected from proteasome-mediated degradation. We hypothesize that Nox1 controls GTPase activity through a redox-dependent regulation of GDI. Indeed, we found that Nox1 KO cells have increased activity of Rac and Cdc42 which was concomitant with an increase in the total levels of these GTPases, suggesting that ROS may control GDI-mediated inhibition of GTPases degradation. In fact, Nox1KO cells have higher levels of GDI and H₂O₂ induces GDI, Cdc42 and Rac1 degradation by 2h while no change in RhoA was observed. Nox1 KO cells also showed an impaired cell migration, polarity and focal adhesion number, all of them can be a consequence of the deregulation of the GTPases levels/activity. The reduction in GDI levels was also observed in animals treated with AngII suggesting an unexplored physiological role for this pathway. Our results show a novel GDI/GTPases redox regulation that may represent a target for future therapeutic.

#7 (morning session)

Implementing EQUIPPED across five VA Emergency Departments

Vandenberg AE, Stevens M, Echt K, Hastings SN, Powers J, Markland A, Hwang U, Hung W, Belbis S, Vaughan C

Background: Challenges inherent in implementing evidence-based practice change may be amplified when implementation occurs across multiple sites. EQUIPPED (Enhancing Quality of Prescribing Practices for Older Veterans Discharged from the ED) is an ongoing multi-component, interdisciplinary quality improvement initiative in five Veterans Affairs (VA) Emergency Department(ED)s to decrease prescribing of potentially inappropriate medications (PIMS) for Veterans over the age of 65. As an integrated national healthcare system, the VA Medical Centers offer a relatively uniform platform for implementation while highlighting site-specific differences.

Methods: We conducted a thematic content analysis of field reports from EQUIPPED sites at team meetings occurring every two weeks from October, 2013, to November, 2014, to compare site implementation. Using an inductive to deductive evaluation process, we subsequently developed an implementation model for EQUIPPED.

Results: Differences in formularies and ED patient makeup resulted in local adaptations of clinical decision support (CDS) tools for avoiding prescription of PIMS. Presence of resident physicians at some EDs required monthly rather than one-time

education sessions. Varying levels of staff availability and expertise resulted in CDS rollout times that ranged from 3 weeks to 12 months.

Conclusions: EQUIPPED is an innovative geriatric prescribing practice intervention whose success is dependent on careful planning and site customization. Distilling factors that differed across VA sites resulted in a model intended for use by non-VA sites wanting to implement the EQUIPPED intervention.

#38 (morning session)

Ebola virus disease, infection control and environmental safety in a biocontainment unit

Varkey JB, Kraft CS, Mehta AK, Lyon GM, Vanairsdale S, Olinger P, Ribner BS

Background: In 2014, four patients with Ebola Virus Disease (EVD) were treated in the Serious Communicable Diseases Unit (SCDU) at Emory University Hospital. Strict infection control practices were implemented to avoid environmental contamination and prevent nosocomial transmission of EVD to healthcare workers.

Methods: All high touch surfaces were wiped at least every four hours using commercially available hospital disinfectant wipes. Body fluids that contacted the patient care area were immediately contained and disinfected using a quaternary ammonium compound (MicroChem, Westborough, MA). After patients with EVD were discharged, but before terminal decontamination using vaporized hydrogen peroxide, environmental samples were obtained from high-touch surfaces using a dacron-tipped swab moistened with bacteriostatic saline. Environmental swabs were tested for the presence of Ebola virus (EBOV) using RT-PCR (Biofire Defense, Salt Lake City, UT). All health care providers who entered the SCDU, laboratory technologists, and anyone managing the waste stream were required to measure their temperature and complete a symptom questionnaire twice daily.

Results: All 9 samples obtained on 3 separate dates tested negative for EBOV by RT-PCR. Samples tested included patient's personal belongings (phone, tablet computer), high-touch areas (call button and bedrails) and the bathroom environment (commode, toilet seat, sink handles, etc). No employee developed Ebola virus disease.

Conclusions: With appropriate protocols and preparation, Ebola virus disease can be managed successfully in a biocontainment unit without causing environmental contamination or occupation related infections. Meticulous attention to infection control practices by a highly motivated, trained and competent staff is critical to the safe care of patients with EVD.

#53 (afternoon session)

Central control mechanisms associated with urinary incontinence in Parkinson's disease

Landry AN, McGregor KM, Crosson B, Nocera JR, Vaughan CP

Objective: To evaluate baseline factors and central control mechanisms associated with urinary incontinence (UI) in persons with early Parkinson's disease (PD).

Methods: Secondary analysis of baseline resting state MRI data from the Parkinson Progression Markers Initiative (PPMI) using cortical and subcortical regions of interest (ROI) with functional connectivity analysis (fcMRI). Explore ROIs of micturition and UI from selected literature to determine their association with UI in PD.

Results: Subjects were men and women ≥ 30 years of age diagnosed with PD within 2 years of the study. The PPMI study included n=423 PD subjects, with n=80 useable resting state MRI. Of the 80 subjects, 20 had UI. Those with UI reported involuntary loss of urine at least 'sometimes in the past month' based upon the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms. Descriptive statistics compared baseline factors of PD subjects with and without UI. The UI population was older and reported more constipation, but there were no differences in gender, medical conditions, depression, cognitive function, or motor symptom severity. Measures of functional connectivity as assessed by fcMRI showed lower network coherence in the limbic monitoring circuit (bilateral insula, putamen, amygdala, and medial frontal region).

Conclusions: In early PD, presence of UI is not associated with motor symptom severity or cognitive function. Resting state fcMRI data suggest PD patients with UI have disrupted limbic monitoring possibly resulting in urinary urgency and subsequent incontinence. These data support the introduction of behavioral therapy in this population for rehabilitative intervention.

#4 (morning session)

Prevalence of advanced colorectal adenomas in patients undergoing screening colonoscopy in a safety-net hospital

Levy S, Vora R, Qayed E

Purpose: Advanced colorectal adenomas are important precancerous lesions. The aim of this study is to measure the prevalence of adenomas and advanced adenomas in African Americans and other racial groups.

Methods: All asymptomatic patients that underwent screening colonoscopy between July 1st 2009 and June 30th 2014 were included in the analysis. Patients with history of polyps, diagnostic or incomplete colonoscopies were excluded. Logistic regression was used to calculate the crude and adjusted odds ratios for the association of colonic findings with African Americans compared to other racial groups.

Results: Among patients with adequate and complete examination (n=6448), 2326 (36%) were men and 4122 (64%)

were women. Mean age was 58 years. The majority of patients were black (n=5691, 88.4%), followed by white (n=334, 5.2%), and Hispanic (n=213, 3.3%). The overall prevalence of adenomas was 32.3%, and advanced adenomas was 8.3%. African Americans had similar rates of advanced adenomas compared to other groups (adjusted OR 1.15, 95% CI 0.9-1.5). There was a higher rate of high grade dysplasia/cancer in African Americans compared with other racial groups (1.4% Vs. 0.5%, adjusted OR 2.9, 95% CI 1.1-8). Rates of non-advanced adenomas, adenomas >9mm, and adenomas with tubulovillous histology were similar.

Conclusion: The prevalence of adenomas with dysplasia/cancer was significantly higher in African Americans. This supports the need for special efforts to improve colorectal cancer screening participation rates in African Americans.

#26 (afternoon session)

Ubiquitin proteasome system in pulmonary hypertension

Wade BE, Hart CM, Sutliff RL

Pulmonary Hypertension (PH) is characterized by the sustained increase in pulmonary arterial pressure. Increased pulmonary vascular pressure and resistance result in right ventricle (RV) hypertrophy and can ultimately lead to RV failure and death. The pathogenesis of vascular cell proliferation and vascular remodeling in PH is incompletely defined. Current therapeutic approaches employ vasodilators but do not address the cellular proliferation and vascular remodeling that underlie the pathogenesis of PH. To more directly address mechanisms of cell proliferation in PH, this research focuses on the ubiquitin proteasome system (UPS) which plays a critical role in cellular homeostasis by regulating protein stability. Current evidence demonstrates changes in UPS activity in PH; however, the proteins and pathways impacted are poorly defined. To identify proteins with altered ubiquitination in response to hypoxia exposure, mice were exposed to normoxic or hypoxic conditions for 3 weeks. Lungs were harvested and the PTMScan® Ubiquitin Remnant Motif (K-ε-GG) Kit was used to precipitate ubiquitinated proteins for analysis by mass spectrometry (MS). 243 proteins were identified with a fold change $\geq \pm 2$. In silico analysis identified proteins that promote cell proliferation. Tax1bp1, Hspa8, Hspb1, and Fhl1 interact with important cellular proliferation pathways and exhibit decreased ubiquitination in lungs from mice exposed to hypoxia, suggesting an increase in their stability in hypoxia. These results using MS and in silico analysis suggest that hypoxia-induced changes in the UPS may impact proteins involved in pathways that regulate cellular proliferation by increasing or decreasing their stability.

#23 (morning session)

Plasma cells are dramatically expanded in bone marrow from SLE patients

Wang X, Ichikawa HT, Sanz I

Systemic lupus erythematosus (SLE) is characterized by an expansion of peripheral blood plasma cells (PCs) and the production of a variety of autoantibodies. In humans, short-lived

and long-lived PCs in BM have been identified based on the expression of CD19 and CD138, that CD19- CD138+ cells are long-lived, while CD19+CD138+ are short-lived PCs. The purpose of this study is to characterize the plasma cell subsets in SLE BM and determine the relative ability of each subset to produce autoantibody. Flow cytometric analysis of the BM PC subsets in 7 patients with SLE, as well as in 5 HC showed that the frequency of all PC subsets within SLE BM were significantly increased as compared to controls ($p = 0.0001$), particularly the expansion of CD19+CD138+ PC, which is tenfold greater than the matching population in HC. Corresponding to the expansion of all PC subsets in SLE samples, with ELISpot assay, we found that whole BM cells from SLE patients have eight folds higher frequency of IgG ASCs, as compared to the HC group. Furthermore, by ELISpot, we determined the capability of different PC subsets to produce IgG against autoantigens, including: 9G4+ VH4-34 antibodies, anti-Ro, anti-Sm, and anti-dsDNA. Our data showed that both CD19- CD138+ and CD19+ CD138+ population produced autoantibodies to target antigens with comparable frequency in most of the tested samples. Taken together, these findings help us to understand the cellular source of different types of autoantibodies and provide a mechanistic insight into the immunopathogenesis of SLE ASCs.

#25 (afternoon session)

Does autophagosome-proteolysis contribute to CKD-induced muscle atrophy?

Wang H, Hassounah F, Wang X

In chronic kidney disease (CKD) loss of myofibrillar proteins results from activation of the ubiquitin-proteasome system (UPS) by forkhead transcription factors (FoxO). Since FoxO simulates both the UPS and autophagy, we hypothesized that autophagosome-induced proteolysis contributes to CKD-induced muscle wasting. In control and CKD mice, we compared two models mimicking exercise: overloading (OL) of the plantaris muscle was achieved by removing gastrocnemius and soleus muscles; and muscle were stimulated by acupuncture plus low frequency electric stimulation (Acu/LFES). In both models, the loss of muscle mass in mice with CKD was suppressed. In muscles of CKD these mice there were increases in mRNAs related to autophagy-lysosomal functions, Bnip3, Atg12, Gabarapl1, LC3II and Beclin-1 plus increases in Bnip3, Beclin-1 and LC3II proteins signifying activation of autophagy. Acu/LFES treatment reversed changes in markers of autophagy in muscles of CKD mice. In control mice, OL increased markers of autophagy and lysosomal-related proteins but to the same extent as in muscles of mice with CKD. When myotubes formed from primary cultures of satellite cells were incubated with 2% uremic serum, autophagy markers increased; acidification of myotubes did not stimulate autophagy markers. In the cultured myotubes, we found that stimulation of the UPS but not autophagy increased the degradation of the myofibrillar proteins, myosin and actin. Thus, autophagy is stimulated in muscles of mice with CKD but the UPS rather than autophagy is the principal mechanism degrading myofibrillar proteins. Resistance exercise (mimicked by OL) prevents muscle atrophy by methods distinct from autophagy.

#13 (afternoon session)

Repeat peroral endoscopic myotomy via same site tunneling: a safe and feasible option

Wehbeh A, Mekaroonkamol P, Cai Q

Per oral endoscopic myotomy (POEM) is a novel endoscopic procedure for achalasia treatment. Due to its novelty and high success rates, a repeat procedure is rarely warranted, making the feasibility and safety of such approach unknown. Here, we report the first case of a repeat POEM done by creating a submucosal tunnel at the same site of a previous attempt. An 84 year old female with type 2 achalasia presented for a POEM procedure. Patient was on her supine position which was the standard practice at our institution. During endoscopy, at the end of submucosal tunneling process, she developed severe hypotension and bradycardia. Thus, the procedure was aborted before myotomy, and hypotension resolved spontaneously. Chest x-ray revealed apical pneumothorax, pneumomediastinum, pneumoperitoneum, and extensive subcutaneous emphysema. Tension capnothoraces was likely the culprit of her hemodynamic instability. Thereafter she underwent multiple Botox injections, which eventually failed in relieving her symptoms. A repeat POEM was done one year later. Esophageal sigmoidization was observed. Submucosal incision was made at the same site of the original tunnel, and surprisingly we didn't encounter submucosal fibrosis. The repeat tunneling at the same submucosal plane felt similar to a native POEM and myotomy was performed uneventfully. Our case is the first to highlight the feasibility and safety of performing a POEM at a location where submucosal dissection was previously done. Hypotension during POEM is a rare complication that should be recognized as a potential result of tension capnothorax, it can however, be managed with close supportive care.

#20 (morning session)

Intermittent PTH treatment induces bone anabolism through regulatory T cells

Yu MC, Robinson JW, Vaccaro C, Tyagi AM, Li JY, Luo T, Adams J, DiPaolo R, Pacifici R

Intermittent PTH (iPTH) treatment increases bone mass in mice and humans by activating Wnt signaling in osteoblast through increased production of the Wnt ligand Wnt10b by bone marrow (BM) CD8+ T cells. We found iPTH to expand BM regulatory T cells (Tregs) by increasing the differentiation of naive CD4+ cells into Tregs. Blockade of Treg expansion in vivo using CD25 Ab or diphtheria toxin treatment blunted the capacity of iPTH to induce Wnt10b production by CD8+ cells, stimulate bone formation and increase bone mass. These finding demonstrate that Treg expansion is required for the bone anabolic activity of iPTH. iPTH treatment increases the sensitivity of naive CD4+ cells to the Treg-inducing factor TGFB, by activating Notch signaling in CD4+ cells via upregulation of Notch ligands on osteoblasts (OBs) and activation of Notch signaling in BM CD4 cells. Notch signaling potentiates the effects of TGFB on the expression of the Treg specific transcription factor FOXP3. We found BM Tregs to block the costimulatory molecules CD80/86

on APCs and consume IL-2 in BM, thus inducing CD8+ cell anergy. Comparing with resting T cells, anergic CD8+ cells produce high levels of Wnt10b at baseline and in response to iPTH. In summary, these findings demonstrate a novel effect of PTH on the differentiation of naïve CD4+ cells into Tregs. Expansion of Tregs is a critical, previously unknown mechanism by which iPTH exerts its bone anabolic activity.

#37 (morning session)

Use of plasma metabolomics at diagnosis to identify metabolic pathways associated with pulmonary tuberculosis (TB) clearance: a pilot study

Chong E, Frediani JK, Alvarez JA, Tukvadze N, Kempker RR, Tangpricha V, Li S, Blumberg HM, Yu T, Jones DP, Ziegler TR

Background: Knowledge of metabolic pathways associated with clearance of *Mycobacterium tuberculosis* (Mtb) in TB disease may provide pathophysiologic insight and identify potential biomarkers. Methods: We studied 61 adults with pulmonary TB disease in Tbilisi, Georgia. Subjects entered the trial within 7 days of initiation of conventional anti-TB drug therapy. Mtb clearance from sputum cultures obtained at 8 weeks was determined. Metabolomics analysis of plasma was performed using high-resolution LC-MS. Individual regression models were analyzed for each detected metabolite with sputum culture conversion at 8 weeks as the independent variable and metabolite intensity as the dependent variable, adjusted for MDR-TB status, diabetes status, body mass index, sex, age, and plasma 25-hydroxyvitamin D level. Statistically significant ($p < 0.05$) metabolites were subsequently analyzed with a high-throughput metabolomics pathway analysis program (Mummichog). Results: After 8 wks of anti-TB drug treatment, 52 subjects (85%) had a negative sputum culture and 9 (15 %) remained culture-positive. Of 5,715 metabolites detected, 251 differed ($p < 0.05$) between subjects with sputum culture conversion to negative versus those remaining positive (130 metabolites were decreased and 121 were increased, respectively). Nine specific metabolic pathways significantly differed between the groups, including cytochrome P450 drug metabolism, glutamate metabolism, aspartate and asparagine metabolism, amino-sugar metabolism, de novo fatty acid biosynthesis, and leukotriene metabolism. Conclusions: In patients with pulmonary TB, plasma metabolomics analysis obtained early after TB diagnosis identified metabolic pathways related to drug metabolism, amino acid/nutrient metabolism and inflammation that differentiated individuals who did or did not become sputum culture-negative for Mtb after 8 weeks.

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Morning Session

9:15 – 10 a.m.

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