Abstract Book

October 28, 2016
Cox Hall Ballroom
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Schedule of Events

8:00 – 8:15 am: Registration and Welcome

8:15 – 8:30 am: Featured Research
Jonathan Colasanti, MD, MSPH (Infectious Diseases): “The HIV care continuum: Looking beyond cross-sectional retention and viral suppression”
Winner of the 2016 Outstanding Scientific Citation Award (Clinical/Translational - Junior Faculty)

8:30 – 9:30 am: Oral Presentation Session I  
Moderator: Kehmia Titanji, PhD
8:30 am: “EQUIPPED Expansion: Results from a multi-site quality improvement initiative to change prescribing practices in VA Medical Center Emergency Departments (EDs)” (Melissa Stevens, MD, Hospital Medicine)
8:45 am: “Role of thyroid hormone in postnatal heart growth” (Lin Tan, PhD, Cardiology)
9:00 am: “Safety, immunogenicity and acceptability of inactivated influenza vaccine delivered by microneedle patch” (Michele Paine, MPH, Infectious Diseases)
9:15 am: “An electrocardiogram-based risk equation for incident cardiovascular disease from the National Health and Nutrition Examination Survey” (Amit Shah, MD, MSc, Cardiology)

9:30 – 10:15 am: Poster Session I

10:15 am – 10:30 am: Featured Research
Jyothi Rengarajan, PhD (Infectious Diseases): “Host biomarkers of tuberculosis immunity”
Winner of the 2015 Outstanding Scientific Citation Award (Basic Science - Junior Faculty)

10:30 am – 11:30 am: Oral Presentation Session II  
Moderator: Cherry Wongtrakool, MD
10:30 am: “Timing of readmissions among U.S. hemodialysis patients” (Laura Plantinga, PhD, Renal Medicine/ General Medicine and Geriatrics)
10:45 am: “NADPH oxidase-2 mediates zinc deficiency-induced oxidative stress and kidney damage” (Clintoria Williams, PhD, Renal Medicine)
11:00 am: “Use of oral agents (DPP4 inhibitors) for the management of patients with type 2 diabetes: Sita-Hospital Trial” (Isabel Anzola, PhD, Endocrinology)
11:15 am: “Predictors of lymph node involvement in early stage gastric adenocarcinoma in the United States” (S. Kusuma Pokala, Digestive Diseases)

11:30 am – 12:00 pm: Featured Research
Roberto Pacifici, MD (Endocrinology): “Microbiota and probiotics: Unexpected bone regulators”

12:00 – 12:15 pm: Group Photo

12:15 pm: Lunch

1:15 pm: Keynote Talk: “So you need a research focus? How about aging?”
Kenneth Covinsky, MD, MPH, University of California, San Francisco

2:15 – 3:00 pm: Poster Session II

3:00 – 3:45 pm: Oral Presentation Session III  
Moderator: Amir Rezvan, MD, MS
3:00 pm: “Isolation of a highly angiogenic subpopulation of CD31+ cells” (Brandon Johnson, Cardiology)
3:15 pm: “B-cell profile as a biomarker of disease segmentation and flare prognosis in SLE” (Chungwen Wei, PhD, Rheumatology)
3:30 pm: “Antioxidants improve lung immunity and T-cell proliferation in immune non-responders” (Sushma Cribbs, MD, Pulmonary)

3:45 – 4:15 pm: Featured Research
Arshed Quyyumi, MD (Cardiology): “Precision medicine: identifying high risk subjects with cardiovascular disease”
Winner of the 2016 R. Wayne Alexander Excellence in Research Accomplishment Award

4:15 – 4:45 pm: Research Accomplishments and Awards Presentation
David S. Stephens, MD, Chair, Department of Medicine; Vice President for Research, Woodruff Health Sciences Center; Chief of Medicine, Emory Healthcare
Ken Covinsky is a graduate of the UCSF Medical School and completed his internal medicine residency at Johns Hopkins. Following residency, he completed a fellowship in General Internal Medicine at Beth Israel Hospital in Boston and a MPH at the Harvard School of Public Health. After spending 4 years on the faculty at Case Western Reserve University, he was recruited back to UCSF in 1998 to develop the research program in the Division of Geriatrics.

Ken is currently the Edmund G. Brown, Sr. Professor of Medicine at UCSF and director of the UCSF Older American's Independence Center. His research focuses on understanding the determinants and outcomes of disability in older persons. He has demonstrated the key role of functional status as a measure of prognosis in older persons, showing that it more strongly predicts health outcomes than medical conditions and laboratory markers. His work has also defined the syndrome of hospital acquired disability, or the processes through which seemingly minor hospitalizations in older persons lead to disability. Ken has devoted a large portion of his effort to mentoring, focused on mentoring clinician investigators in geriatrics and sub specialist investigators who are working on aging related issues in their specialty. He has received several awards for research mentorship including the Society of General Internal Medicine MidCareer Mentorship award, and the UCSF Hal Luft Award for mentoring in health services and policy research.
Oral Presentations

8:30 am

EQUiPPED expansion: results from a multi-site quality improvement initiative to change prescribing practices in VA Medical Center Emergency Departments (EDs)


Background: EQUiPPED is an ongoing multi-component, interdisciplinary quality improvement initiative in eight Veterans Affairs EDs. Results for EQUiPPED at the first site have been described previously. This abstract describes results from three additional VA EDs to implement EQUiPPED.

Methods: EQUiPPED uses the VA-TAMMCS process improvement framework and aims to decrease the use of potentially inappropriate medications (PIMs), as identified by the Beers list, prescribed to Veterans aged ≥65 years at the time of ED discharge. Interventions include: 1) provider education; 2) informatics based clinical decision support with EMR-embedded order sets and links to online geriatric content; and 3) individual provider audit and feedback, and peer benchmarking. Data were examined at each site for six months pre-EQUiPPED, throughout the implementation phase, and for at least six months post-intervention at four sites. Poisson regression was used to compare the number of PIMs prescribed to Veterans aged 65 years and older discharged from the ED before and after EQUiPPED.

Results: Table 1 shows results from 4 sites.

Table 1: Average Monthly Proportion of PIMs

<table>
<thead>
<tr>
<th>Site</th>
<th>Pre-EQUiPPED</th>
<th>Post-EQUiPPED</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlanta</td>
<td>11.8 (SD 1.8)</td>
<td>5.3 (SD 1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Birmingham</td>
<td>8.9 (SD 1.9)</td>
<td>6.3 (SD 1.4)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Bronx</td>
<td>7.4 (SD 1.7)</td>
<td>5.6 (SD 1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Durham</td>
<td>8.3 (SD 0.8)</td>
<td>4.5 (SD 1.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions: EQUiPPED led to a significant and sustained reduction of PIMs prescribed to older Veterans at the first four implementation sites and suggests that the program could be successfully disseminated throughout the VA system.

9:00 am

Safety, immunogenicity and acceptability of inactivated influenza vaccine delivered by microneedle patch


Background: Microneedle patches provide an alternative to traditional intramuscular delivery of influenza vaccine that offers multiple potential advantages, including immunogenicity (targeting skin, an immunologically rich site), simplicity (amenable to self-vaccination), cost-effectiveness (reducing costs of vaccine administration, cold chain and sharps waste disposal), and safety (eliminating needle-stick injuries).

Methods: A phase 1, partially blinded, placebo-controlled, randomized clinical trial was conducted to assess safety, reactogenicity, immunogenicity and acceptability of trivalent inactivated influenza vaccine delivered by a dissolvable microneedle patch or by hypodermic needle. Microneedle patches were applied by healthcare worker or by self-administration.

9:45 am

Role of thyroid hormone in postnatal heart growth

Tan L, Berce M, Naib H, Caesar C, Husain A, Naqvi N

Introduction: 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.

Methods: Cardiomyocytes (CMs) were isolated from postnatal day (P)-1 to 2 hearts and subsequently treated with T3, vehicle or PEG-catalase under serum free conditions. CMs were then collected for western blot analysis and qRT-PCR. Hydrogen peroxide was measured by AmplexRed assay. P2 to P7 mice were injected with Tempo along with T3 or vehicle and ventricular CM numbers were measured at P7. ANOVA or t-test was used for comparison between groups.

Results: T3 increased the expression of cyclin D1 and 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 IGF-1. T3-dependent IGF-1 expression results in activation of pro-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 increased 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, 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.

Conclusion: We conclude that T3 functions as a cardiomyocyte mitogen in early postnatal cardiomyocytes through H2O2/IGF-1/pErk signaling.
Conclusions: The use of a dissolvable microneedle patch for influenza vaccination administered by healthcare worker or by subjects themselves was well-tolerated, preferred and resulted in robust antibody responses.  

9:15 am

An electrocardiogram-based risk equation for incident cardiovascular disease from the National Health and Nutrition Examination Survey

Shah AJ, Vaccarino V, Janssens AC, Flanders WD, Kundu S, Veledar E, Wilson PW, Soliman EZ

Introduction: Electrocardiography (ECG) may detect subclinical cardiovascular disease (CVD). We attempted to derive and validate a CVD risk equation based on ECG metrics and to determine its incremental benefit in addition to the Framingham risk score (FRS).

Methods: We studied 3640 community-based adults aged 40 to 74 years without known CVD from the First National Health and Nutrition Examination Survey (NHANES I) cohort (1971-1975) and 6329 from the NHANES III cohort (1988-1994). A risk score was derived in NHANES I based on frontal P, R, and T axes; heart rate; and PR, QRS, and QT intervals. The most prognostic variables, along with age and sex, were incorporated into the NHANES ECG risk equation. The equation was evaluated in the NHANES III cohort. The primary end point was CVD death.

Results: 100 healthy subjects naïve to 2015-2016 seasonal influenza vaccine (age 18-49 years) were enrolled after influenza season between June and September 2015. There were no related serious adverse events and no related grade 3 or higher clinical or laboratory adverse events. Reactogenicity was mild and transient, and exhibited similar incidence among vaccinated groups, most commonly reported as tenderness and pain after intramuscular injection and tenderness, erythema and pruritis after microneedle patch application. Among subjects vaccinated by microneedle patch, geometric mean titer, seroconversion rate and seroprotection rate determined by hemagglutination inhibition antibody assay were significantly higher at D28 compared to placebo and were comparable to intramuscular injection. Microneedle patches were preferred compared to intramuscular injection in >70% of subjects.

Conclusions: The use of a dissolvable microneedle patch for influenza vaccination administered by healthcare worker or by subjects themselves was well-tolerated, preferred and resulted in robust antibody responses.

10:30 am

Timing of readmissions among U.S. hemodialysis patients

Plantinga LC, Lea J, Patzer RE, Jaar B

Background: In 2017, U.S. dialysis facilities will be accountable for hospital readmissions within 30 days. Earlier readmissions provide fewer chances for dialysis providers to intervene and may also be predictive of poor outcomes. We examined the prevalence of hospital readmissions and compared 1-year mortality by timing of readmission.

Methods: We identified 153,349 U.S. hemodialysis (HD) patients from a national registry (United States Renal Data System) who had at least one hospitalization in 2010 (first-index) and survived on HD for at least 30 days. Timing of readmissions was defined by admissions within 0-7, 8-14, or 15-30 days after discharge from the index admission. Multivariable Cox proportional hazards models were used to estimate the association between timing of readmission and mortality within 1 year.

Results: Overall, 13.1%, 5.9%, and 9.6% of patients had readmissions within 0-7, 8-14, and 15-30 days of discharge from index admission; 45.8% of readmissions were within 7 days. Compared to those without readmissions, patients with readmissions had about twice the risk of death within 1 year, with adjustment for age, sex, race/ethnicity, dialysis vintage and comorbid conditions: 15-30 days, HR=2.05 (95% CI, 1.98-2.12); 8-14 days, HR=2.06 (95% CI, 1.97-2.15); and 0-7 days, HR=1.80 (95% CI, 1.74-1.86).

Conclusion: Nearly half of 30-day readmissions occurred within the first 7 days after discharge, suggesting that dialysis providers often have a limited opportunity to prevent readmission. These results also suggest that readmission, regardless of timing, is associated with about 2-fold increased risk of mortality in the following year among U.S. HD patients.
determine the role of these enzymes in ZnD-induced oxidative stress. We hypothesized that ZnD promotes Nox upregulation resulting in oxidative stress and kidney damage. To test this hypothesis, WT mice were pair-fed a ZnD- or Zn2+ adequate-diet. Kidney damage, ROS generation and Nox expression were examined. To further investigate the effects of Zn2+ bioavailability on Nox regulation, mouse tubular epithelial cells (mTEC) were exposed to the Zn2+ chelator N,N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) or vehicle followed by Zn2+ supplementation. The findings show that mice fed a ZnD-diet develop microalbuminuria and kidney hypertrophy that are accompanied by elevated Nox2 expression and H2O2 levels. In mTEC, TPEN-induced ZnD is accompanied by elevated H2O2 levels. In this in vitro model of ZnD, Nox inhibition with diphenyleneiodonium (DPI) prevents H2O2 generation. Furthermore, TPEN-induced Nox2 expression and activation are reversed with Zn2+ supplementation. Knock-down of Nox2 prevents TPEN-induced H2O2 generation and cellular hypertrophy, indicating that these effects are Nox2 mediated. Taken together, these findings reveal that Nox2 is a Zn2+-regulated enzyme that mediates ZnD-induced oxidative stress and kidney hypertrophy. Understanding the mechanisms by which ZnD contributes to kidney damage may have an important impact on the treatment of CKD.

11:00 am

Use of oral agents (DPP4 inhibitors) for the management of patients with type 2 diabetes: Sita-Hospital Trial


Objective: This multicenter randomized clinical trial was designed to compare the safety and efficacy of a DPP4-inhibitor (sitagliptin) plus basal insulin vs. basal bolus insulin regimen in the management of general medicine and surgery patients with type 2 diabetes (T2D).

Methods: A total of 280 patients with blood glucose (BG) between 140-400 mg/dl and treated with diet, oral antidiabetic agents or total daily insulin dose ≤0.6 unit/kg were randomly allocated (1:1) to receive sitagliptin plus glargine once daily or to basal bolus regimen with glargine once daily and lispro before meals. Major outcomes included differences in mean daily BG and frequency of hypoglycemia between treatment groups.

Results: There were no differences in the mean daily BG (170±49 mg/dl vs. 169±48 mg/dl, p=0.96), proportion of BG readings 70-180 mg/dl (57% vs. 60%, p=0.58), hospital length of stay (median [interquartile range]: 4 [3-8] vs. 4 [3-8] days, p=0.54) or in a composite of hospital complications including acute kidney injury, wound infection, stroke, acute myocardial infarction, respiratory failure, reoperation, and pneumonia (10% vs. 8%, p=0.66) between sitagliptin-basal and basal-bolus groups. The total daily insulin dose (0.24±0.14 U/kg vs. 0.33±0.16 U/kg) and number of daily insulin injections (2.2±1.1 vs. 2.9±0.9) were less in the sitagliptin-basal vs. basal-bolus, both p<0.001. There were no differences in the number of patients with hypoglycemia (9% vs. 12%, p=0.45) between groups.

Conclusion: Treatment with sitagliptin plus basal insulin is safe, effective and more convenient than basal bolus regimen for the management of general medicine and surgery patients with T2D.

11:15 am

Predictors of lymph node involvement in early stage gastric adenocarcinoma in the United States

Pokala SK, Chen Z, Gamboa A, Keilin S, Cai Q, Willingham FF

Introduction: Endoscopic resection is being used increasingly in the United States and may be offered for the treatment of early gastric cancers; however, the propensity of early stage tumors to spread to lymph nodes in the US population is not well defined. This study examined the incidence of nodal metastasis for early stage (T1a and T1b) low grade gastric adenocarcinoma in the US.

Methods: Data was extracted from the national SEER database from 2004-2013. Chi-square and logistic regression tests were used to analyze the relationship of tumor stage, grade, size, race and age with nodal metastasis. Low grade included well or moderately differentiated tumors.

Results: 43,769 total cases of gastric adenocarcinoma were initially identified and after exclusions, 1,828 cases of early stage adenocarcinoma were analyzed. Multivariate analysis revealed that T1b tumors had a higher rate of nodal metastasis than T1a tumors (p<.001), high grade tumors had a higher rate than low grade tumors (p<.001), and tumors ≥4cm had a higher rate than tumors <1cm (p<.001). Of low grade T1a tumors, 1.6% at 0-2cm, 4.2% at 2-3cm, 6.0% at 3-4cm, and 20% at ≥4cm had nodal metastasis (p<.001).

Conclusion: Tumor stage, grade and size are significant predictors of nodal metastasis in early stage gastric adenocarcinoma in the US. For larger, higher grade, T1b tumors, the rate of nodal metastasis is high and lymph node dissection should be considered for good surgical candidates. Low-grade T1a tumors <4cm have low rates of nodal metastasis and may warrant consideration for endoscopic resection.

3:00 pm

Isolation of highly angiogenic subpopulations of CD31+ cells

Johnson BAL, Sohn YD, Jun HW, Yoon YS
Critical limb ischemia (CLI), a state of unrelenting rest pain and ulceration in peripheral limbs has an amputation and mortality rate of 40% and 20%, respectively for patients without revascularization options. Due to a projected increase in incidence of CLI, it is imperative to develop alternative therapies for revascularization. Recently, our lab has shown that CD31+ cells are a heterogeneous population of highly angiogenic cells found circulating in peripheral blood; however, the exact mechanism of these cells’ effectiveness and the contribution of the cellular subtypes is currently unknown. We hypothesize that CD31+ cells initiate angiogenic, proliferation of endothelial cells, and arteriogenic, recruitment of mural cells, properties through their CD14+ and CD14- subpopulations, respectively. To test our hypothesis, we isolated CD31+CD14+ (13+14+) and CD31+CD14- (13+14-) cells from human peripheral blood and used qRT-PCR to show that angiogenic factor VEGFA was increased in 13+14+ cells while arteriogenic factors FGF2, PDGFB, CXCR4 and TGFb are increased in 13+14- cells. To determine therapeutic effects, 13+14+ and 13+14- cells stained with CM-Dil were injected into the ischemic hindlimbs of athymic nude mice. After 4 weeks, mice were perfused with FITC-Bs1 lectin and sacrificed. Histology shows that mice injected with 13+14+ cells have greater capillary formation than 13+14- cells while mice injected with 13+14- cells show greater engraftment of transplanted cells and recruitment to blood vessels. In conclusion, 13+14+ cells express an angiogenic expression profile and induce capillary growth in vivo while 13+14- cells express arteriogenic markers and show perivascular homing in vivo.

3:15 pm

**B cell profile as a biomarker of disease segmentation and flare prognosis in SLE**


B cell abnormalities in SLE are well-established contributors to disease pathogenesis. Perturbation of B cell homeostasis in SLE is often described separately for each affected B cell subset independent of others. Such univariate approaches fail to reveal how collections of subsets and their relative distribution might contribute to patient segmentation. Hence, we sought a global B cell profiling approach in conjunction with comprehensive clinical parameters to identify distinct B cell signatures in SLE. High dimensional flow cytometry analysis identifies three major clusters of SLE patients based on the B cell profiles. Cluster 1 is characterized by an activated B cell profile and is significantly enriched with patients who present high SLEDAI, multiple autoantibodies and elevated serum IFNα activity, and who are of African descent. In contrast, patients in cluster 3 exhibit a B cell profile that is similar to that of healthy controls and are least likely to present a high disease activity. To evaluate the application of B cell profiling in predicting future lupus flare, low-SLEDAI, non-flaring patients from each cluster at baseline were followed for flare incidences. Preliminary results show that inactive patients with an activated B cell profile appear to have a higher propensity to develop a flare sooner. Our results provide a proof of concept that, when combined with other informative clinical parameters, B cell profiling offers a systems biology approach to identifying potential biomarkers to estimate risk of disease progression and to initiate early treatment that might halt disease progression or improve long-term outcome.

3:30 pm

**Antioxidants improve lung immunity and T-cell proliferation in immune non-responders**

*Cribbs SK, Brown LA, Paiardini M, Kraft C, Rimland D, Lennox J, Marconi V, Guidot DM*

Background: HIV-1 immune non-responders are at increased risk for lung infections. Alveolar macrophages (AMs) can be infected by HIV-1. We have shown that HIV-1-infected individuals have zinc and glutathione deficiency, that HIV within AMs impairs phagocytic function, and in vitro supplementation of zinc and glutathione improves phagocytic function. We hypothesize that dietary zinc and S-adenosylmethionine supplementation will enhance AM immune functions and reduce AM viral burden in immune non-responders.

Methods: HIV-1 immune non-responders were given zinc and S-adenosylmethionine daily and underwent bronchoscopy and blood sampling pre-treatment and after 12 months. AM phagocytic index (% positive cells x mean channel fluorescence/100) was measured using FITC-labeled S. aureus. Proviral DNA was measured using a modified Abbott RealTime HIV-1 Assay (Abbott Molecular Inc. Des Plaines, IL). Immunologic parameters were analyzed by flow cytometry.

Results: We enrolled 14 HIV-1 infected subjects (median CD4 count=257/μl) with viral suppression. AM phagocytosis increased with treatment (31.4% + 43.9, p=0.02). HIV-1 proviral DNA was detected in 5/14 patients initially and all were negative after treatment. There were no significant changes in frequencies of CD4 and CD8 T cells, their maturation subsets or frequencies of T cells expressing activation markers (HLA-DR and CD38). There was a significant reduction in frequencies of CD4 (p<0.001) and CD8 (p=0.04) T-cell proliferation, as assessed by Ki-67 expression.

Conclusions: In HIV-1 infected immune non-responders, dietary supplementation with zinc and S-adenosylmethionine reduced T cell proliferation, improved AM phagocytosis and may improve HIV-1 clearance from the lung, potentially reducing the risk for lung infections.
#28 (afternoon session)

**Low prevalence of clinically significant endoscopic findings in outpatients with dyspepsia**

*Abdeljawad K, Wehbeh A, Qayed E*

**Background:** The value of endoscopy in dyspeptic patients is questionable.

**Aims:** Examine the prevalence of clinically Significant Endoscopic Findings (SEF) and the utility of Alarm Features, and age≥55 in predicting SEFs in dyspeptic outpatients.

A retrospective analysis of outpatients who had an endoscopy between June/2011 and July/2015 was done for dyspeptic patients ≥18 years. Demographic variables, pertinent medications, alarm features, and endoscopic findings were recorded. We defined SEF as P UD, erosive esophagitis, malignancy, stricture, or other finding requiring therapy. Chi-square test of independence was performed to examine the association of endoscopic findings with alarm features. Multivariable logistic regression was performed to calculate the aOR for the association of alarm features and age ≥55 with SEFs.

**Results:** Of the 650 patients who met the inclusion criteria, 51% had a normal endoscopy. The most common endoscopy abnormality was non-erosive gastritis (29.7%) followed by non-erosive duodenitis (7.2%) and LA-class A esophagitis (5.4%). Only 10.2% had a SEF. Five patients (0.8%) had malignancy. SEF was more likely to be in patients with alarm features compared to those without (12.7% Vs 5.4%, p=0.004). Age ≥55 and presence of any alarm features were associated with SEFs (aOR 1.8 and 2.3 respectively).

**Conclusion:** Dyspeptic patients have low prevalence of SEF. The presence of any alarm features and age ≥55 is associated with higher risk of SEF. Endoscopy in patients with no alarm features and <55 years has a low yield. Patients with no alarm features who are <55 years can be considered for non-endoscopic approach.

#20 (afternoon session)

**Comparison of efficacy and safety of glargine and detemir in the management of inpatient hyperglycemia and diabetes**

*Alfa D, Galindo R, Davis G, Fayfman M, Pasquel FJ, Umpierrez GE*

**Objective:** We compared the safety and efficacy of glargine and detemir insulin therapy in hospitalized patients with hyperglycemia and diabetes.

**Research Design and Methods:** This was a retrospective two-center study of hospitalized non-ICU patients with hyperglycemia and diabetes admitted between 01/01/2012 and 09/30/2015. De-identified data was collected from electronic medical records. ICD-9 codes were used to identify study variables.

**Results:** Of the 6,245 patients included, 5,749 patients were treated with glargine and 496 with detemir during their hospital stay. There were no differences in the mean
hospital blood glucose (BG) between glargine and detemir groups (glargine: 182±46 mg/dl vs detemir: 180±44 mg/dl, p=0.70), number of patients with BG > 250 mg/dl (70% vs 69% p=0.56), hypoglycemia (< 70 mg/dl, 34% vs 30%, p= 0.08), severe hypoglycemia (< 40 mg/dl, 5% vs 5%, p=0.88) or nocturnal hypoglycemia (10% vs 11%, p= 0.47). In addition, no differences were observed in the number of hospital complications (42% vs 42%, p=0.89) or readmissions (3.3% vs 4.6%, p=0.13) between groups. Patients treated with detemir required higher insulin dosage (0.27±0.16 vs 0.22±0.16 units/kg/day, p=0.001) and number of injections (1.14±0.27 vs 1.07±0.20, p <0.001); and patients treated with glargine had longer hospital length-of-stay (6.8±7 vs 6.0±6 days, p<0.001).

Conclusions: Our study indicates that insulin glargine and detemir are equally safe and effective in improving glycemic control in hospitalized patients with hyperglycemia and diabetes in non-ICU settings. A prospective randomized control trial is needed to confirm these preliminary findings.

#33 (afternoon session)

Regulation of T cell antigen receptor (TCR) signaling thresholds for T cell proliferation

Activation of T cell immune responses requires transduction of biochemical signals initiated by the T cell antigen receptor (TCR). These signals are triggered within seconds of TCR recognition of antigenic peptide/MHC, yet T cells require hours or days of TCR stimulation to elicit some hallmarks of T cell activation or function. So how much TCR stimulation do T cells require, and when do they require it? To address this question we take advantage of a recently developed transgenic reporter mouse called Nur77-GFP. This transgene consists of GFP under the transcriptional control of the Nr4a1 (Nur77) promoter, an immediate/early gene responsive to antigen receptor signals but not cytokine signals. Using this system, we show that dividing T cells express a minimum amount of GFP, which we interpret as a TCR signal threshold for T cells must reach to proliferate. Despite variation of the magnitude of TCR stimulation provided, the amount of GFP expressed (TCR signaling) by T cells that proliferated remained above the apparent threshold. Surprisingly however, we found that provision of the T cell growth factor IL-2 could lower the apparent TCR signal threshold for CD8+ T cells but not CD4+ T cells. We attribute this biological difference to a delay in the capacity of CD4+ T cells to sense IL-2. These studies show that other signaling inputs such as cytokine signals, can potentially impact how different amounts of TCR signaling are required depending on the inflammatory cues present in the cellular environment.

#48 (morning session)

Different strengths of T cell antigen receptor signaling are experienced by CD4+ T cells undergoing Th1, Th2 and Th17 differentiation
Cheng D, Basso V, Chen Y, Weiss A, Au-Yeung B

We recently developed and characterized a chemical-genetic experimental system in which a bulky analog of the small molecule inhibitor PP1 can specifically inhibit the catalytic kinase activity of an 'analog-sensitive' mutant of Zap70 (called Zap70 (AS) here). Due to the essential function of Zap70 in transmitting signals from the T cell antigen receptor (TCR), this system enables control of TCR signaling. In this study we aimed to determine the relative contribution of varying Zap70 activity to the lineage decisions of naïve CD4+ T cells. In response to TCR stimulation in the presence of graded concentrations of a Zap70(AS) inhibitor but without exogenous polarizing cytokines, we observed diminished frequencies of cells capable of producing effector cytokines. However, titration of Zap70 activity did not alter the relative propensity of T cells to produce Th1 (IFNgamma) versus Th2 (IL-4) cytokines, suggesting that titration of TCR signal strength in this manner did not cause a switch in CD4+ T cell differentiation programs. Unexpectedly, the generation of IL-17 producing Th17 cells was more susceptible to inhibition of Zap70 activity relative to the generation of IFNdelta producing Th1 cells and IL-4 producing Th2 cells. The increased sensitivity of T cells undergoing Th17 differentiation to Zap70 inhibition suggests that the level of Zap70 expression and/or the level of Zap70 catalytic activity are factors that influence CD4+ T cell differentiation. We conclude that T cells undergoing Th17 differentiation experience weaker signals, rendering them more sensitive to inhibition of TCR signals.

#59 (morning session)

Psycho-behavioral correlates of physical activity in veteran dyads with physical dysfunction
Bailey RR, Griffiths PC

Purpose: To identify factors associated with physical activity of caregivers and care-recipients in veteran dyads.

Methods: Physical activity, measured in activity counts, was assessed using wrist-worn accelerometry in 30 veteran dyads where care-recipients experienced physical dysfunction. The outcome of interest was ∆Counts, calculated by subtracting mean daily activity counts of care-recipient instrumental activity of caregivers and care-recipients in veteran dyads.
activities of daily living (CR-IADLs), caregiver time commitment, and caregiver burden. Descriptive and analytic statistics were used to examine relationships between \( \Delta \)Counts and factors of interest.

Results: \( \Delta \)Counts was moderately-to-strongly correlated with all factors of interest (Pearson correlation coefficients ranged from -0.78 to 0.67, \( p<0.05 \)). Significant differences between dyads in the top versus bottom 50th percentile of \( \Delta \)Counts were observed for all factors. Caregiver activity counts, care-recipient sleep duration, CR-IADLs, caregiver time commitment, and caregiver burden were significantly higher while care-recipient activity counts and caregiver sleep duration were significantly lower in dyads in the top 50th percentile (for all values, \( p<0.02 \)).

Conclusions: Increased \( \Delta \)Counts was associated with increased activity counts and decreased sleep duration in caregivers, whereas the opposite was true for care-recipients. The inverse relationship between physical activity and sleep in caregivers may be partially explained by increased caregiver responsibilities, whereas the relationship in care-recipients may be moderated by dependence in IADLs. Increased physical activity at the cost of decreased sleep in both caregivers and care-recipients bears further exploration.

#1 (morning session)

Osteogenic effects of nanoparticles are composition, size, and surface dependent

Ha SW, Habib MM, Weitzmann MN, Beck GR

The advent of nanotechnology has provided new opportunities to engineer biomaterials of novel size and composition, leveraging the nanoscale to enhance biological responses. The excitement surrounding the potential applications of nanotechnology to medicine in part revolves around the almost unlimited possibilities for varying the physicochemical properties with greatly increased surface area and differential cell recognition relative to the bulk form. We have leveraged multiple synthetic methods and material choice in engineering nanoparticles (NPs) for manipulation of bone metabolism. Our previous studies have identified that 50 nm silica NPs can enhance bone mineral density in growing mice and can reverse age-associated bone loss in old mice. These NPs have been demonstrated to have a favorable therapeutic index, in vitro, of \(~ 500 \sim 1000\) with minimal toxicity suggesting a high safety profile. The NPs function in vitro by promoting the differentiation of bone forming osteoblasts while inhibiting the differentiation of bone resorbing osteoclasts. The aim of this study was to determine if 50 nm silica nanoparticles are the optimal size and nanomaterial composition for bone benefit. Towards this end, a range of silica NPs (30 - 450 nm) with different surface properties (OH, COOH, PTMA, and DETA) were tested along with various NPs of different composition (gold and polystyrene) but the same shape and size (50 nm-spherical) for enhancement of osteoblast differentiation in vitro. The optimal NP for enhancement of osteoblast differentiation and mineralization was identified as a spherical NP of silica composition in the critical range of 50 to 100 nm.

#44 (morning session)

PPAR\( \gamma \) agonists attenuate biofilm formation by *Pseudomonas aeruginosa*


*Pseudomonas aeruginosa* is a significant contributor to recalcitrant multi-drug resistant infections especially in immunocompromised and hospitalized patients. 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 *P. aeruginosa* secretes small diffusible molecules, specifically acyl homo serine lactones (AHL) such as 3O-C12-HSL that promote biofilm formation and virulence via inter-bacterial communication. Strategies that strengthen host’s ability to inhibit bacterial virulence would enhance host defenses and improve treatment of resistant infections. We have recently shown that Peroxisome proliferator-activated receptor (PPAR\( \gamma \)) agonists are potent immunostimulators and play a pivotal role in host response to virulent *P. aeruginosa*. Here we show that QS genes in *P. aeruginosa* (PAO1) and C12-HSL attenuates PPAR\( \gamma \) expression in epithelial cells. PAO1 and C12-HSL induced barrier derangements in BEAS-2B cells by lowering expression of barrier proteins such as Occludin and ZO-1. Expression of these proteins was restored in cells pretreated with pioglitazone (PIO) a PPAR\( \gamma \) agonist, prior to infection with PAO1 and C12-HSL, indicating the ability of PPAR\( \gamma \) agonists to restore barrier integrity. These effects were dependent on the induction of Paraxonase-2 (PON-2) a QS hydrolyzing enzyme, thus enhancing cellular of clearance of PAO1. PIO significantly inhibited biofilm formation on epithelial cells, thus indicating a functional impact of PON-2 induction by PPAR\( \gamma \). These findings elucidate a novel role for PPAR\( \gamma \) in host defense. Strategies that activate PPAR\( \gamma \) can provide a therapeutic complement for the treatment of resistant *P. aeruginosa* infections.
Impact of fluid therapy on clinical outcomes in acute pancreatitis: time to revisit the guidelines?

*Berger S, Body C, Leer-Greenberg B, Yang X, Sakaria S, Qayed E, Chawla S*

Early fluid resuscitation is the cornerstone of management in acute pancreatitis. Management guidelines recommend early aggressive hydration to improve clinical outcomes. The aim of this study is to evaluate the influence of IVF in the first 24 and 48 hours (hrs) on organ failure, ICU transfer, and mortality. We performed a retrospective chart review of all patients admitted to Grady Memorial Hospital with acute pancreatitis between 7/2011 - 12/2015. The total amount of IVF given at 24 hours was categorized based on tertiles (< 2.8L, 2.8-4.475L, and >4.475L), and hourly IVF infusion rates as follows (<100ml, 100-199 ml, and ≥200 ml/hr). BMI, BISAP score at admission, and Charlson Comorbidity index were recorded as they can independently impact clinical outcomes. There were 280 patients during the study period. Mean age was 46 years, and median BMI was 26.8. Patients in the highest tertile of total IVF and hourly IVF rate had significantly increased risk of ICU transfer and organ failure, compared to patients receiving lower IVF amounts and rates. There was no difference in mortality among the different IVF groups. Multivariate logistic regression analysis found every 1L increase in IVF at 24 and 48hr was associated increased risk in ICU transfer, organ failure and mortality. Our study shows an association with poor outcomes in patients receiving higher IVF volumes and rates during the early treatment period for acute pancreatitis. These results are similar to other recently published studies, and do not support the current guidelines.

Higher Mediterranean diet quality score and lower BMI are associated with a less oxidized plasma glutathione and cysteine redox status in adults

*Bettermann EL, Hartman TJ, Ferranti EP, Jones DP, Quyyumi AA, Vaccarino V, Ziegler TR, Alvarez JA*

Background: Both plasma redox and diet quality are associated with chronic disease risk, although the extent to which diet quality influences plasma redox status is unknown. We aimed to investigate the relationships of diet quality and obesity on systemic thiol/disulfide redox status.

Methods: We performed a cross-sectional study of 721 working adults in Atlanta, Georgia. Diet quality was assessed by diet quality scores of habitual dietary intake derived from Block food frequency questionnaires (the Alternative Healthy Eating Index (AHEI), the Dietary Approaches to Stop Hypertension (DASH) Score, and the Mediterranean Diet Score (MDS)). We measured plasma glutathione (GSH), cysteine (Cys), and their respective oxidized forms and redox potentials to assess redox status. Linear regression modeling was performed to assess relationships, independently of body mass index (BMI) and other confounders.

Results: The MDS was positively associated with plasma GSH ($\beta=0.03$, $p<0.05$) and negatively associated with the cystine/GSH ratio ($\beta=-0.03$, $p<0.05$) in multivariate models. Individual Mediterranean diet components (dairy, vegetables, fish, and monounsaturated fat) were also significantly associated with plasma redox outcomes ($p<0.05$). AHEI and DASH indexes and other dietary factors were not significantly associated with plasma redox outcomes. Obesity status was significantly associated with more oxidized plasma redox markers and several dietary factors, including diet quality indexes and sulfur amino acid intake ($p<0.05$).

Conclusion: Adherence to a Mediterranean diet was associated with less oxidizing plasma thiol/disulfide redox systems, while obesity was associated with a more oxidizing state. These findings contribute to the feasibility of targeting diet to improve plasma redox status.

Evaluating the relationship between hemoglobin A1C and gastric, small bowel, colonic, and whole gut transit


Introduction: Gastroparesis and constipation are well known gastrointestinal (GI) complications of long standing diabetes mellitus (DM). There is a paucity of data regarding the correlation between hemoglobin A1c (A1c) and gastric, small bowel, colonic, and whole gut transit.

Methods: Subgroup analysis of data from a cohort of diabetic patients with chronic idiopathic constipation was performed. Demographics and A1c measurements were obtained. Gastrointestinal transit was evaluated utilizing the pH motility capsule (Smartpill®). A comparison between GI transit times in diabetics with controlled (A1c <7) and uncontrolled (A1c ≥ 7%) diabetes was made.

Results: 76 patients were included in the parent study and 34 had their A1c evaluated within 3 months of enrollment and an adequate pH motility capsule study. There is no statistically significant difference in gastric, small bowel, colonic, and whole gut transit in patients with controlled versus uncontrolled diabetes ($p>0.05$). However, there is a trend toward longer transit times in those with lower A1c.
mean gastric transit (14.6 vs. 7.8 hours p=.14) and mean whole gut transit (64.6 vs. 52.7 hours p=.17) in those with controlled versus uncontrolled diabetes, respectively.

Discussion: This study did not find a statistically significant relationship between A1c and gastric, small bowel, colonic, or whole gut transit. It is possible that daily glycemic control is more likely to affect GI transit. Additionally, given that A1c reflects the average blood sugar over the prior 3 months, a normal A1c may not reflect previous neurological damage from uncontrolled diabetes.

#35 (morning session)

Evaluating the effect of Lubiprostone on small bowel transit time as measured by SmartPill® in a predominantly African-American population of diabetics with constipation: randomized, double-blind, placebo-controlled trial


Introduction: Constipation is the most common gastrointestinal symptom in patients with diabetes mellitus (DM). Many patients with chronic constipation have prolonged small bowel transit times (SBTT) and some diabetics have also been found to have prolonged SBTT. Lubiprostone’s effect on SBTT in healthy patients as measured by video capsule endoscopy is unclear due to conflicting data. However, lubiprostone has recently been studied to improve colonic transit time as measured by SmartPill® in diabetics with constipation.

Methods: Diabetic patients with chronic idiopathic constipation (CIC) were recruited from outpatient clinics as part of a larger study. Demographic information was obtained and baseline SBTT was evaluated utilizing the pH motility capsule (Smartpill®). Patients were randomized in a double-blind fashion to 48 mcg/day lubiprostone or placebo for 8 weeks. A follow-up Smartpill® was performed after 4 weeks of therapy.

Results: 76 patients were enrolled and 42 were included in this analysis. There were no significant differences between the two groups’ demographics or baseline data. Following 4 weeks of therapy, neither patients in the lubiprostone group (5.13±1.58 vs. 6.08±1.974 hours, p=0.47) nor the placebo group (5.85±2.32 vs. 4.9±1.08 hours, p=0.34) experienced a significant change in SBTT from baseline. The change in SBTT from baseline in the treatment group was not significantly different than the change in SBTT from baseline in the placebo group (0.95±2.68 vs. -0.96±2.01 hours, p=0.25).

Discussion: This study suggests lubiprostone has no significant effect on SBTT in patients with DM and CIC.

#57 (morning session)

What do decisions makers feel is a good outcome?

Preliminary results of end of life decision making survey

Buchanan KB, Lava MS, Dickert NW, Frew PM, Martin GS, Sevransky JE

Rationale: Little is known about which outcomes patients and surrogates value in the ICU.

Objective: To identify what patients and surrogate decision makers consider a “good” outcome in the setting of life threatening critical illness.

Methods: We screened patients admitted to three ICUs at Emory University Hospital meeting criteria for sepsis and/or the Acute Respiratory Distress Syndrome (ARDS). Interviews with the patient and/or surrogate decision maker were conducted in the ICU, and transcribed and scored based on responses to four specified outcomes.

Measurements and main results: 33 patients were enrolled with a total of 43 total interviews between patients and surrogates. 100% of patients and surrogates considered “discharge home and return to work” as a good outcome. 71% of patients and 75% of surrogates considered “discharge home, unable to work” a good outcome. 36% of patients and 54% of surrogates deemed “discharge home with significant help in activities of daily living” a good outcome. 0% of patients and 12% of surrogates consider “discharge to a nursing home” a good outcome.

Conclusion: The majority of patients and surrogates considered discharge home, either with or without return to work, as a good outcome. Few surrogates and no patients considered discharge to a nursing home a good outcome. Surrogate decision makers considered all outcomes to be “good outcomes” at higher rates than patients.

#42 (morning session)

Understanding the role of the RLR pathway in SLE disease pathogenesis

Cashman KS, Sanz I

Antiviral signaling is an essential immunologic process necessary for the identification, communication, and eradication of foreign virion derived material. At the forefront of most antiviral responses is the production of type-I interferons (e.g. IFNα and IFNβ). Type-I interferon responses have a multitude of upstream activation
receptors/sensors, of which toll-like receptors, NOD-like receptors, cytosolic DNA sensors, and RIG-I-like receptors (RLR) constitute the dominant protein families. Interestingly, many autoimmune disorders such as systemic lupus erythematosus (SLE) exhibit aberrant elevations of type-I IFN production and signaling, which is thought to play a key role in the disease pathogenesis. Targeting these antiviral pathways in the context of autoimmunity was stumbled upon following World War I when the use of antimalarials (e.g. hydroxychloroquine) was shown to benefit patients suffering from SLE; and it was subsequently determined that these drugs interfered with TLR activation. Hydroxychloroquine is still widely used today for SLE, but has shown to be less than optimal in the control of disease manifestations. Given the activation pathway redundancy in the production of type-I interferons we chose to examine manifestations. Upon qPCR analysis it was determined that members of the RLR family were significantly increased in PBMCs from patients with SLE as compared to healthy individuals. Protein expression levels by FACS validated these findings and isolated one of the primary contributing cell types as being B cells; a finding backed by qPCR on the purified B cells population.


This study examined differences in resource utilization and hospitalization costs in Black and White patients with hyperglycemia and diabetes admitted to Emory University between 1/2012 and 12/2013. Patients were categorized according to three glycemic groups: non-DM with normoglycemia (BG < 180 mg/dl), non-DM with hyperglycemia (BG ≥ 180 mg/dl), and known diabetes (DM). Of 29,422 patients, 12,171 (41.4%) were Black and 17,251 (58.6%) were White. When compared to Whites, Blacks were younger (60±17 vs 65±16 yrs), had higher BMI (29.8±9 vs 28.1±7), and had a higher frequency of DM compared to Whites (35% vs.24%, p<0.001). Blacks had more comorbidities including hypertension and chronic kidney disease and had more hospital complications including acute myocardial infarction, stroke, pneumonia, urinary tract infection, and acute kidney injury, all p<0.001. Mortality was not different between groups, p=0.42. Compared to Whites, Blacks had lower overall costs (median [IQR] $12,082 [6,251-22,247] vs $16,364 [8,955-28,721], p<0.001), as well as less laboratory tests, consultations, and pharmacy resource utilization (all p<0.001). Costs of hospitalization was significantly higher in Whites compared to Blacks independent of glycemic status —costs being higher for non-DM with hyperglycemia ($29,276 [16,231-49,380] vs. $23,536 [12,318-45,866], p<0.001), DM ($15,353 [8,465-28,630] vs. $11,481 [5,884-21,203], p<0.001), and non-DM with normoglycemia ($13,718 [7,694-22,402]) vs $10,505 [5,561-17,543], p<0.001). These differences persisted in the multivariate analysis adjusted for demographics, insurance coverage, complications, and comorbidities. The study showed that despite a higher rate of complications, Black patients have lower hospitalization costs and resource utilization compared to Whites.


Executive dysfunction is commonly identified in hypertensive older adults, but the underlying neural basis for this dysfunction is poorly understood. Resting state functional magnetic resonance imaging (rsfMRI) has shown a promise to delineate the neural connectivity underlying brain functions and dysfunctions. Here we seek to examine the rsfMRI patterns of directed interactions among three functional neural networks: default-mode network (DMN), salience network (SN), and central-executive network (CEN) in older adults with hypertension and executive dysfunction and compare this interaction to a sample of cognitively normal older adults. All subjects underwent rsfMRI and the obtained images were analyzed using spatially constrained independent component analysis. Directed interaction between the target networks was assessed using dynamical causal modelling (DCM) analysis which infers the causal architecture of network interactions. We used t-test to compare the two groups. In contrast to cognitively normal older adults, in whom SN exhibit controls over the DMN and the CEN (t-test p<0.05; FDR-corrected), older adults with hypertension and executive dysfunction exhibit disruption in this control by SN over the other networks (p<0.01; FDR-corrected). Further, the degree of disruption in SN-based control is correlated with lower cognitive performance on global testing (Pearson’s correlation; p<0.05). Our study offers a new insight into the neural basis for the observed association between hypertension and executive dysfunction. Namely, that the disruption of SN ability to switch-on-switch-off neural networks at rest. Further investigation into effect of antihypertensive treatment on this observation may offer explanation for the positive effect of antihypertensive medications on cognition.
#47 (morning session)

Human IgE plasma cells in the blood, nasal polyp, and the bone marrow long lived plasma cell subset


Serum IgE antibodies are responsible for asthma and allergy. IgE serum titers are often high in asthmatic or allergic patients, even in the absence of stimuli (i.e. aerocellergens), implying that IgE-secreting plasma cells might be maintained over time. In mice, IgE plasma cells have been shown to be short-lived and are not detected in the bone marrow (BM). The aim of this study is to identify the cellular origins of human IgE and whether high IgE serum levels are sustained by ongoing generation of short-lived plasma cells (SLPC) or if a subset of long-lived plasma cells (LLPC) exists in specific survival niches, acting as a continuous source of IgE antibodies. We track the cellular source of human IgE in the nasal polyp, blood, and both SLPC or LLPC compartments of BM. We demonstrated that the frequency of circulating IgE ASC is higher in allergic or asthmatic patients compared to healthy donors and increase during the allergy season. IgE-specific ASC frequencies are higher in NP compared to any other tissue and the majority of IgE transcripts are found in the most immature PC subset (POP 2, CD19+CD38hiCD138-). In the nasal polyps IgE ASC sequences are connected to NP Naive sequences but not to the blood B cell subsets, suggesting a local IgE class switch recombination. In the BM, IgE-specificity is found in SLPC (pop A: CD19+CD38hiCD138- & pop B: CD19+CD38hiCD138+), but also in the LLPC subsets (pop D: CD19-CD38hiCD138+).

#36 (morning session)

Outcomes and quality of life assessment after gastric per oral endoscopic pyloromyotomy (G-POEM)

Dacha S, Li L, Mekaroonkamol P, Shahnaz N, Keillin S, Willingham FF, Christie J, Cai Q

Introduction: Gastric Per oral endoscopic pyloromyotomy (G-POEM) is emerging as an option for treatment of refractory gastroparesis. The purpose of this study is to assess outcomes and improvement in quality of life after G-POEM.

Methods: We performed a retrospective review of data for patients who underwent G-POEM. All pertinent pre-procedural data (demographics, etiology of gastroparesis, gastroparesis cardinal score index (GCSI), four hour gastric emptying scan (GES) and prior treatments), procedural data (procedure duration, length of myotomy, adverse events, length of hospitalization), and post-procedural GCSI and GES data were abstracted. A short form 36 (SF36) obtained pre and post G-POEM procedure was analyzed. Clinical success was defined by improvement in clinical symptoms measured by a decrease in GCSI and no recurrent hospitalization. Normally distributed data were analyzed using a paired t test. SF-36 was expressed as medians and analyzed using the Wilcoxon signed-rank test. A p value less than 0.05 was considered statistically different.

Results: A total of ten patients with refractory gastroparesis underwent the procedure (diabetic in four patients (40%), idiopathic in four patients (40%), one post infectious (10%) and one post-surgical (10%) at our institution between June 2015 and May 2016. Of these, eight were female (80%) and two were male patients (20%). Four patients were African American (40%) and six patients were Caucasian (60%). Mean age was 47.3+/- 17.3 years. Mean BMI was 24.3+/- 5.9 kg/m2. Mean duration of procedure was 47.7+/-20.1 minutes. Mean myotomy length was 2.94+/- 0.1 cm. Mean length of hospital stay was 2.5 +/ -0.9 days. No adverse events occurred with G-POEM. Overall, the procedure was clinically successful in eight out of ten patients (80%) during a mean follow up of 4.6 months+/-4.1 months (range 1-12) with a decrease in mean GCSI from 30.1+/-4.6 prior to the procedure to 12.8+/- 8.7 (p=0.0001) at follow up. Post G-POEM GES was obtained on 7 patients (normalized in 5 patients and improved in 2 patients) Mean 4-hour gastric retention on GES decreased from 62.5 % +/- 24.4 to 25.4 % +/-19.3 (p=0.009) after G-POEM. One patient had no response and required hospitalization for nausea and vomiting 15 days after G-POEM, and one patient did not have improvement in her symptoms. SF-36 questionnaire demonstrated a significant improvement in quality of life in several domains during follow up (Figure 1).

Conclusion: This study demonstrates promising short-term outcomes after G-POEM for gastroparesis with significant relief of symptoms in most, not all patients, measured by an improvement in GCSI score, reduced gastric retention percentages on 4 hour GES and significant improvement in several domains of the quality of life assessment.

#24 (afternoon session)

Stress hyperglycemia and risk of perioperative complications and mortality in nondiabetic patients undergoing general surgery

Davis GM, Fayfman M, Reyes D, Pasquel FJ, Vellanki P, Haw S, Umpierrez GE

This study aimed to determine the prevalence and clinical outcome of stress hyperglycemia, defined as a blood glucose (BG) > 140 mg/dL, in surgery patients without a history of diabetes at 4 university-affiliated hospitals. A total of 424 patients (21.2%) developed ≥ 1 episode of hyperglycemia with BG>140 mg/dL and 220 patients (11%) with BG>180 mg/dL within 48 hours after surgery. Patients with stress hyperglycemia had significantly higher rates of complications: 32% of those with BG>140 mg/dL and 47%
with BG>180 mg/dL compared to 22% of patients with BG <140 mg/dL. Compared to patients with normoglycemia (all BG≤140 mg/dL), patients with stress hyperglycemia, BG>140 and >180 mg/dL, had a longer length of hospital stay (LOS) (median LOS of 9 and 11.5 days, respectively) vs. 6 days in patients with normoglycemia, p<0.001. Mortality in patients with stress hyperglycemia was 2% for BG>140 mg/dL, 5% for BG>180 mg/dL compared to 1% in patients with normoglycemia, p<0.001. After adjusting for age, gender, BMI and race, compared to patients with normoglycemia, those with stress hyperglycemia had more complications (odds ratios (OR) 1.98 (95% CI: 1.51-2.61)) and higher mortality [2.82 (0.93-8.56)]. Complications and mortality were even higher in patients with postoperative BG>180 mg/dl (OR 3.36 (2.39-4.71) and 8.05 (2.92-22.17) respectively). Development of stress hyperglycemia in non-diabetic patients undergoing surgery is common and is associated with longer LOS, and increased rates of hospital complications and mortality. Randomized clinical trials are needed to determine if treatment of stress hyperglycemia can improve outcomes in surgery patients.

#32 (afternoon session)

Acute and long term cognitive and neuroanatomical changes in adult patients recurrent episodes of diabetic ketoacidosis (DKA)


Poor treatment adherence is the precipitating factor in 2/3 of patients with recurrent diabetic ketoacidosis (DKA). To test the hypothesis that recurrent DKA is associated with cognitive impairment leading to poor treatment adherence, we conducted a pilot study assessing cognitive function and structural brain changes in adult patients with 1st DKA (n=10), recurrent >3 DKA (n=10), DM without DKA (n=10), structural brain changes in adult patients with 1st DKA we conducted a pilot study assessing cognitive function and cognitive impairment leading to poor treatment adherence, test the hypothesis that recurrent DKA is associated with of patients with recurrent diabetic ketoacidosis (DKA). To study recurrent DKA were included in this study. To determine if recurrent DKA is associated with cognitive impairment and altered brain structure, which may lead to poor treatment adherence and repeated hospital admissions with decompensated diabetes. Larger studies are needed to confirm the observed DKA-induced neurotoxicity and cognitive impairment and to design interventions to prevent recurrent DKA.

#18 (afternoon session)

A case of acute on chronic arsenic toxicity secondary to betel nut usage

*Dudgeon MR*

A 26 year-old Nepali woman presented with worsening epigastric pain and bilateral lower extremity pain. She had recently been diagnosed with gallstones and had no other significant past medical history. Her initial history was limited by altered mental status and presenting exam was notable for tachycardia and epigastric tenderness. She was found to be acidotic (pH 7.10) with sodium 120, BUN 72, SCr 11.1, lactic acid 2.5, total bilirubin 12.7, corrected calcium 6.4 and lipase 122. CT abdomen showed distended gallbladder without stones and hepatic steatosis, while bilateral lower extremity Doppler was negative for thrombosis. Her mental status improved and her metabolic derangements normalized with volume replacement and bicarbonate. Nursing staff discovered remains of betel nut and Areca in her bed. Further history-taking revealed chronic betel nut and Areca use continuing during hospitalization, and her leg pain was revealed to be burning of the soles of her feet. Serum was tested for lead, mercury, cadmium, and arsenic, and urine was tested for lead and arsenic; the patient was found to have normal serum levels of heavy metals but elevated urine levels of arsenic. The patient was encouraged to discontinue betel nut and Areca use. Areca is a psychostimulant, and use has been associated with heavy mental poisoning. This patient's acidosis and neuropathy were ultimately attributed to arsenic poisoning associated with her Areca usage. This patient's case demonstrates the importance of careful history taking and physical exam, cultural sensitivity, and broad differential diagnoses for toxic metabolic illness.

#8 (morning session)

TFN-α alters intra- & extracellular isomiR profiles of endothelial cells

*Dvalishvili M, James AM, Rooney K, Searles CD*

Coronary artery disease alters intracellular/extracellular expression & release of microRNAs (miRs). MiRs modulate pro-anti-inflammatory genes & variations in miR profiles are due to transport issues & shifts in isomiR profiles. TNF-α alters the expression of select miRs in human aortic endothelial cells (HAECs) & their release into microvesicles (MVs). Inhibitors (caspase-3 inhibitor [CASP-i] & RhoA Kinase inhibitor [ROCK-i]) target EC MV-involved
release pathways. We hypothesized that TNF-α & MV pathway inhibitors alter the levels of select isomiRs in HAECs & EC MVs. Using qRT-PCR, intracellular & MV levels of seven isomiRs (isomiR-10b,-30d,-93,-143,-181a,-182, & -744) were quantitated in HAECs treated with TNF-α ± CASP-i & ROCK-i. MVs were isolated from these HAECs & quantitated by flow cytometry. Among all treatment groups, the abundance of isomiR-10b,-143,-181a, & -744 was 10-10,000 fold higher in cells versus MVs. Dissimilarly, the abundance of isomiR-30d & -182 was 10-100 fold higher in EC MVs versus HAECs. TNF-α only increased the intracellular levels of isomiR-181a (P<0.05; 0.016). CASP-i alone increased HAECs level (100-10,000-fold) HMR of isomiR-10b&-143. However, ROCK-i alone only increased isomiR-182 in EC MVs. Co-treatment with TNF-α +CASP-i (P<0.05; 0.027) or TNF-α +ROCK-i (P<0.05; 0.017) increased intracellular isomiR-181a levels. Moreover, co-treatment with TNF-α +ROCK-i or TNF-α +CASP-i increased isomiR-30d levels in EC MVs vs. HAECs. These data provide insight into the relationship between the intracellular expression of isomiRs & their extracellular release in response to MV-involved release pathways.

#3 (afternoon session)

Relationship between coronary microvascular dysfunction and coronary epicardial atherosclerotic and endothelial disease in patients with non-obstructive coronary artery disease

Esteherardi P, Hung OY, Corban MT, Gogas BD, Mehta PK, Shaw LJ, Quyyumi AA, Samady H

Background: While CMD has been implicated as a marker of early or diffuse CAD, the relationship between CMD and epicardial disease remains undefined.

Methods: Seventy-seven patients with non-obstructive CAD (fractional flow reserve [FFR] > 0.75) underwent coronary angiography, intravascular ultrasound (IVUS), and invasive Doppler velocity and pressure measurements of the left coronary artery. Adenosine-induced hyperemic microvascular resistance (HMR) was calculated as ratio of distal pressure to average peak velocity (CMD = HMR ≥2.0 mm Hg/cm/s) and FFR as ratio of distal to proximal pressure. Diffuse epicardial CAD was quantified based on the percentage of IVUS frames with plaque burden ≥50% (PB: plaque area/vessel area × 100). Minimum, median, and maximum of PB for each vessel was calculated. Thirty of these patients also underwent epicardial endothelial function assessment by percentage change in coronary diameter in response to intracoronary acetylcholine (endothelial dysfunction = increase in diameter ≤20%).

Results: Compared to patients with normal microvascular function, those with CMD (39% of patients) had higher minimum, median, and maximum PB (p<0.05 for all) as well as higher percentage of IVUS frames with PB≥50% (5 [0, 39]% vs. 26 [6, 54]%, p=0.024) suggesting more diffuse CAD. Moreover, Log-HMR correlated with Log-minimum PB (r=0.261, p=0.02) in the entire population. There was no significant difference in prevalence of endothelial dysfunction (82% vs. 89%, p=NS) or percent diameter change (9.8% vs. 8.8%, p=NS) between patients with or without CMD.

Conclusions: In patients with non-obstructive CAD, CMD is associated with greater burden of plaque and more diffuse epicardial CAD.

#39 (morning session)

Antagonistic interactions between TGFβ1 and Nrf2 in the alveolar epithelium of HIV-1 transgenic rats

Fan X, Statieh B, Raynor R, Guidot DM

We have used HIV-1 transgenic (HIV-1 Tg) rats to elucidate the mechanisms by which chronic exposure to HIV-related proteins seen in people living with HIV alters the alveolar microenvironment, i.e. low levels of glutathione, epithelial barrier dysfunction, and impaired macrophage phagocytic capacity in their alveolar space. Recently we identified that Nrf2, the master transcription factor required to induce the programmatic expression of anti-oxidant defenses, is inhibited in the alveolar epithelium of HIV-1 Tg rats. Therefore, we sought to determine if chronic HIV-1 Tg expression induces TGFβ1 within the alveolar epithelium and if this could be mechanistically involved in the impairment of anti-oxidant defenses in individuals living with HIV. Primary rat alveolar epithelial cells were isolated from HIV-1 Tg and wild type rats. HIV-1 Tg rats had increased expression of TGFβ1 and decreased expression and activity of Nrf2 in the alveolar epithelium. Direct treatment of naïve alveolar epithelial cells with TGFβ1 in vitro likewise decreased the expression and activity of Nrf2, and impaired barrier formation. In parallel, RNA silencing of Nrf2 expression increased TGFβ1 expression and decreased epithelial barrier integrity. Interestingly, the deleterious effects of TGFβ1 on anti-oxidant defenses and barrier integrity could be antagonized by co-treating cells with the Nrf2 activator sulforaphane. In summary, chronic HIV-1 Tg expression induces TGFβ1, which can antagonize the protective actions of Nrf2 in the alveolar epithelium. Activating Nrf2 with phytochemicals such as sulforaphane antagonizes these pathophysiological effects of TGFβ1 and might be a novel method of enhancing lung health in individuals living with HIV.

#47 (afternoon session)

Integration of multi-omics data reveal dynamic oxidative stress responses to manganese in human SH-SYSY neuroblastoma cells

Fernandes J, Uppal K, Chandler JD, Lili LN, Hu X, Go YM, Jones DP

Manganese (Mn) occurs naturally in the environment at low doses and is essential for normal cellular processes. Excessive occupational Mn exposure also causes oxidative
stress and neurotoxicity with symptoms similar to Parkinsonism, creating an unusual requirement that Mn intake must be optimized to maintain homeostasis. We therefore employed a dose response design with human neuroblastoma SH-SY5Y cells to gain a mechanistic understanding of mitochondrial-cellular signaling networks generated in response to Mn varied over a physiologic to minimally toxicological range. We treated cells with different MnCl₂ doses for 5h and found that cellular Mn accumulation was similar to literature values for human brain at ≤10 μM and increased to toxicological concentrations at ≥50 μM. Mn had dynamic effects on mitochondrial activity. Mn increased mitochondrial hydrogen peroxide (H₂O₂), antioxidant superoxide dismutase activity and oxidation of protein thiols in a dose dependent manner. In addition, data analysis from multi-omics platform including high resolution mass spectrometry-based metabolomics, transcriptomics by RNA-sequencing, and redox proteomics by redox isotope coded affinity tag-based mass spectrometry was performed. Results show that Mn significantly altered 262 metabolites, 567 transcripts and 100 protein peptides. Central hubs altered by Mn include mitochondrial dysfunction, oxidative stress responses, energy metabolism, protein folding, cytoskeleton remodeling, tyrosine and butanoate metabolism. Together, we show that mitochondrial oxidative signaling and cellular neurotransmitter metabolism respond dynamically to different Mn levels. Such changes in the mitochondria could be critical determinants to complex cellular signaling that either protect or exacerbate the emergence of neurological disorders.

#49 (morning session)

Frew PM, Fisher AK, Basket M, Chung Y, Schamel J, Weiner J, Mullen J, Omer SB, Orenstein WA

Background: There is growing public health concern on stabilizing “vaccine confidence” (i.e., vaccine hesitancy) in the wake of recent high-profile outbreaks of vaccine preventable diseases (VPDs). We examined timely detection of shifts in vaccine confidence.

Methods: We conducted a national poll of parents of children <7 years in 2012 and 2014 on vaccine decisions. We calculated survey-weighted population estimates of overall immunizations decisions, and delay/refusal rates for specific vaccines.

Results: In 2012, 89.2% (95% CI, 87.3–90.8%) reported accepting or planning to accept all recommended non-influenza childhood vaccines, 5.5% (4.5–6.6%) reported intentionally delaying one or more, and 5.4% (4.1–6.9%) reported refusing one or more vaccines. In 2014, the acceptance, delay, and refusal rates were 90.8% (89.3–92.1%), 5.6% (4.6–6.9%), and 3.6% (2.8–4.5%), respectively. Between 2012 and 2014, intentional vaccine refusal decreased slightly among parents of older children (2-6 years) but not younger children (0-1 years). The proportion of parents working to catch up on all vaccines increased while those refusing some but not all vaccines decreased. The South experienced significant increase in estimated acceptance (90.1% to 94.1%) and a significant decrease in intentional ongoing refusal (5.0% to 2.1%). Vaccine delay increased in the Northeast (3.2% to 8.8%).

Conclusions: Acceptance and ongoing intentional delay of recommended non-influenza childhood vaccines were stable. These findings suggest that more effort is warranted to counter persistent vaccine hesitancy, particularly at the local level. Longitudinal monitoring of immunization attitudes is also warranted to evaluate temporal shifts over time and geographically.

#54 (afternoon session)

Use of clinical decision aids to increase living donor kidney transplantation
Gander JC, Gordon EJ, Patzer RE

Kidney transplantation is the preferred treatment to end stage renal disease (ESRD) offering improved quality of life, longer survival, and lower hospitalization rates compared to dialysis. With >636,000 adults with ESRD, the gap between the demand for kidneys and the number of organs available continues to widen. Living donor kidney transplantation (LDKT) comprised 33% of kidney transplantations in 2013, a 7% decrease since 2004. Decision aids are evidence-based tools designed to help patients and their families participate in making specific choices, such as living donation, among healthcare options. The 11 identified decision aids encompass a variety of topics such as providing patients with communication tools to discuss LDKT with their social network, educating patients and potential donors on the financial aspects of LDKT, enhancing patients’ knowledge about the survival benefits of transplant versus dialysis, and discussing the health risks to potential living donors. While many decision aids have been developed to assist patients, from different cultural backgrounds, to choose between LDKT and other treatment options, there has been a lack of standardized methods to develop of the decision aids and a lack of dissemination of decision aids. To address the large variation in LDKT across transplant programs, we encourage researchers to dedicate more resources to dissemination and implementation while collaborating with other regions to test the decision aid’s effectiveness in different populations.
Introduction: Cardiac allograft vasculopathy (CAV) following heart transplantation is the “Achilles heel” of long-term transplant survival. Hyperlipidemia, found in 74% of heart transplant recipients in the first year, is associated with CAV development. Notably, this risk is mitigated by statin therapy. Despite evidence supporting statins to prevent CAV, it is unclear if their benefits result from favorable effects on lipids or alternative, immunologic mechanisms. The role LDL lowering specifically plays in CAV prevention remains unclear. We hypothesize that lower mean LDL will result in less CAV.

Methods: A single center, retrospective analysis of 84 consecutive heart transplant recipients between October 2006 and December 2011 surviving a minimum of 1 year was conducted. Demographic data, catheterization results, and laboratory results were collected at each annual visit for up to 5 years or until death. CAV was categorized as grade 0-3 per ISHLT guidelines. The primary outcome assessed was freedom from CAV.

Results: Of the 84 patients, 40 (48%) developed CAV after a mean follow-up of 3.7 years. Mean LDL was 81.7 mg/dL in those without CAV during the study period, compared to 100.4 mg/dL in those who developed CAV (p = 0.008). Freedom from CAV was worse in patients with mean LDL above 90 mg/dL compared to those below 90 mg/dL. In a multivariable Cox regression model incorporating age, gender, diabetes, and hypertension, higher LDL was associated with higher risk for CAV.

Conclusion: Higher mean LDL is associated with higher risk for developing CAV following heart transplantation.

Evaluation of bias in patient enrollment in a study to identify types of end of life decision makers

Garala P, Treki Y, Lava MS, Dickert NW, Frew PM, Martin GS, Sevransky JE

Rationale: To identify potential bias in patient enrollment in a study to identify types of end of life decision makers.

Objective: To compare enrolled patients and patients screened but not enrolled to ensure there are no statistically or clinically significant differences between the two groups.

Methods: We screened patients admitted to two Intensive Care Units at Emory University Hospital meeting criteria for Sepsis and/or the Acute Respiratory Distress Syndrome. Interviews with the patient/surrogate decision maker were conducted based on a convenience sample. SOFA scores and Charlson Comorbidity Index (CCI) were calculated on the day of interview. Mean values of patients who were screened and enrolled were compared to those screened but not enrolled using a student's t-test.

Measurements and Main Results: Mean SOFA score for screened, non-interviewed patients was 6.07 (SD=3.14) compared to 7.24 (SD=3.02) for interviewed patients (p=0.01). Mean CCI was 4.95 (SD=2.62) for screened, non-interviewed patients compared to 5.30 (SD=2.89) for interviewed patients (p=0.01).

Conclusion: Interviewed patients had a both a higher SOFA score and CCI compared to screened, non-interviewed patients, which was statistically significant. Absolute differences were small and were unlikely to have clinical significance.

Racial and sex differences in associations between activities of daily living and CLOX scores in community-dwelling older adults

Garrett SL, Kennedy RE, Sawyer P, Williams CP, Allman R

Background/Objective- Identifying culturally sensitive methods to accurately identify cognitive/functional disability in primary care for older African Americans is needed (as dementia is often undiagnosed). This analysis aimed to examine if there exists association between day-to-day function measured by activities of daily living (ADL) and cognition measured by CLOX scores among older African American (AA) and non-Hispanic White (nHW) community-dwelling women and men.

Design- Cross-sectional study assessing associations between self-reported ADL difficulty and CLOX scores for race/sex specific groups. Setting- Homes of community-dwelling older adults. Participants- 893 Medicare beneficiaries > 65 living in west-central Alabama, part of the University of Alabama at Birmingham (UAB) Study of Aging, excluding those with diagnoses of dementia or missing data. Measurements- Function, assessed via self-reported difficulty completing ADL. Cognition assessed via CLOX, developed by Royall using a fifteen item scoring process. Multivariable, linear regression models were used for statistical analysis.

Results- After controlling for socio-demographic factors and comorbidities, CLOX 1 scores were inversely and significantly correlated with ADL for AA men. CLOX 2 scores were similarly associated with ADL and IADL for the total group; for ADL, significant associations were seen for AA men and nHW women and, for IADL, in AA women and men.
Conclusion- An association exists between ADL and cognition measured by CLOX scores among older AA & nHW community-dwelling adults.

#55 (afternoon session)

Using area under the curve as a decision tool for cytomegalovirus viral load management for kidney transplant patients

Gibby AC, Mehta A, Gander J

Chronic kidney disease (CKD) can lead to end-stage renal disease (ESRD), which is the form of CKD where life can be maintained only by dialysis or transplantation. Transplantation has more benefits compared with chronic disease treatment. There is a significantly lower mortality associated with transplantation, and quality of life is better among transplant recipients. However, the current organ shortage is a limiting factor and it is crucial to ensure and protect the graft from rejection. Cytomegalovirus (CMV) is one of the most prevalent virus after transplantation that can cause significant morbidity, organ rejection, and adverse transplant outcomes. Patients with Donor (+)/Recipient (-) or (+): High Risk and Donor (+)/Recipient (-) or (+): Moderate Risk) and compared different immunosuppressive treatments and CMV viral load (amount of virus) in this population using area under the curve (AUC). Our study found a significant association between CMV high risk (Donor positive/Recipient negative) having a higher AUC in comparison to moderate risk (Donor negative/Recipient positive or Donor positive/Recipient positive). Results indicate no statistical significance among the different immunosuppressive treatments: Belatacept 1.0/1.1, Belatacept 2.0, Belatacept 2.2, Belatacept 2.3, and Tacrolimus 1.5 related, to CMV measurements. In summary, developing AUC and applying data capture, as an analytical tool will support clinical operations to monitor transplant patients focusing on the high-risk groups and having efficient resource allocation.

#11 (morning session)

Very late vasomotor responses and gene expression profiles of porcine coronary arteries at 4 years after deployment of the everolimus-eluting bioresorbable vascular scaffold and the everolimus-eluting metallic Xience V stent.


Background: Early vasomotor responses of arteries treated with 1st gen. bioresorbable scaffolds are restored at 1y. There is a paucity of studies addressing very late functional and machanobiologic responses of arteries treated with next generation metallic or bioresorbable platforms.

Methods: Ten Absorb BVS and 6 Xience V (XV) DES were implanted in the coronaries of 6 non-atherosclerotic Yucatan mini swine, followed-up at 4y. In vivo: In-segment % mean lumen diameter (MLD) changes, following infusion of vasomotor agents were estimated. Ex vivo: Isolated coronary rings were placed in a tension apparatus within a tissue chamber. Tension was measured using a force transducer. Gene Analysis: Gene analysis was performed in explanted coronary arterial segments using the MetaCoreTM Key Pathway Advisor.

Results: In vivo: BVS segments showed significantly different % in-scaffold vasoconstriction after acetylcholine compared to in-stent XV arterial segments at 4 years: -35.5 ± 25.3% vs. -5.1 ± 17.7%, (p=0.035). BVS arteries demonstrated similar constrictive responses to control: -35.5 ± 25.3% vs. -54.4% (p=0.496). Ex vivo: Endothelial-dependent % relaxation induced by substance P, of BVS vs. XV arteries within the scaffolded/stented segments was significantly different at 4 years: 59.05 ± 29.34% vs. 12.44 ± 24.88%, (p=0.007). Gene analysis: Gene analysis indicated that the Lymphotoxin-beta receptor pathway is upregulated in XV stented arteries enhancing the transcription of genes that encode vascular cell adhesion molecules and interleukins.

Conclusion: Very late functional responses of BVS treated arteries are fully restored. Genetic analysis suggests sustained inflammatory expression even 4 years after XV metallic stent deployment.

#6 (afternoon session)

Conformability and wall shear stress assessment following deployment of the resolute integrity zotarolimus-eluting stent and the XIENCE Xpedition everolimus-eluting stent in angulated vessels: an interim analysis of the SHEAR-STENT randomized controlled study


Background: Given its continuous wire molding and sinuosoidal design, we hypothesized that Resolute Integrity stent (R-ZES) is more conformable than the XIENCE Xpedition stent (X-EES) and therefore may induce more physiologic wall shear stress (WSS) in angulated coronary arteries.

Methods: Interim analysis of angiographic (angio) and intravascular ultrasound (IVUS) acquisitions of patients from the SHEAR STENT study (n=25/126), randomized to R-ZES (n=12) vs. X-EES (n=13) deployment in vessels ≥30° angulation was performed. In-segment % change in
Results: In the whole cohort (n=25), vessel angulation decreased from 49±23° to 33±21°, (p=0.008), a percentile change of -35±28%, suggesting significant vessel straightening. R-ZES was more conformable than X-EES, demonstrating less straightening of angulation 53±28° to 39±22°, (p=0.183) vs. 47±18° to 27±19°, (p=0.012) and of curvature 1.45 ± 0.64 cm-1 to 1.18 ± 0.51 cm-1 (p=0.273) vs 1.4± 0.7cm-1 to 0.8±0.3cm-1, (p=0.022) respectively. In a small subset of 6 patients, we did not observe significant differences in mean WSS within stented segments or at the proximal and distal edges. (Figure)

Conclusions: R-ZES appears to be more conformable than X-EES in angulated coronary arteries. The hemodynamic significance of better conformability, and its effect on neointimal growth at 1 year follow up, remains to be elucidated at completion of the study.

#60 (afternoon session)

MicroRNA-21 and PDCD4 mediate antiproliferative effects of PPARγ in hypoxia-exposed human pulmonary artery smooth muscle cells

Green DE, Murphy TC, Hart CM

Purpose of Study: Pulmonary hypertension (PH) is a complex disease whose cellular pathogenesis involves enhanced smooth muscle cell (SMC) proliferation and resistance to apoptosis signals. Programmed cell death (PPCD) 4 stimulates apoptosis, and its depletion is associated with dysregulated cancer cell growth and metastasis. However, little is known about PPCD4 expression and regulation in pulmonary vascular smooth muscle cells. The current study examines interactions between PPARγ, miR-21 and PPCD4 to further explore antiproliferative mechanisms of PPARγ.

Methods: HPASMC protein and mRNA levels were measured using Western blotting and qRT-PCR, respectively in HPASMC exposed to normoxic or hypoxic conditions. HPASMC were also transfected with an adenoviral PPARγ-expressing plasmid (AdPPARγ,10 MOI) ± activation with 10 uM RSG. Proliferative responses of HPASMC to hypoxia, PPARγ overexpression or PPCD4 and PPARγ depletion were determined. MiR expression was quantified.

Results: Hypoxia increased HPASMC miR-21 expression, reduced PPCD4 protein and mRNA levels and blunted PPCD4 luciferase reporter activity. AdPPARγ attenuated hypoxia-induced: a) reductions in PPCD4 activity, b) increases in miR-21 levels, c) reductions in PPCD4, and d) HPASMC proliferation. SiRNA-mediated depletion of PPARγ or PDCD4 reduced PDCD4 protein levels and enhanced HPASMC proliferation.

Conclusions: Loss of PDCD4 drives proliferation in hypoxia-exposed HPASMC, and PPARγ activation inhibits HPASMC proliferation in part by restoring PDCD4 levels. These findings are consistent with previous reports that PPARγ activation favorably regulates a spectrum of proliferative signals in the pulmonary vascular wall thereby providing a novel potential therapeutic target in PH.

#58 (afternoon session)

Paracrine effects of satellite cells on collateral vessel formation
Hansen L, Joseph G, Weiss D, Taylor WR

Peripheral artery disease is a major health problem that leads to limb pain, decreased mobility, and in severe cases, amputation. The ability to form robust collateral networks to restore blood flow leads to a better prognosis and restoration of function. The growth of collaterals is a complex process that involves the migration and proliferation of various cells regulated by numerous paracrine signals. We hypothesize that a novel source of these signals is satellite cells, myogenic progenitor cells. We hypothesized that activated satellite cells produce factors that will influence critical cells for vessel formation. To study the paracrine effects of satellite cells on vascular smooth muscle cells, we used a co-culture system with freshly isolated satellite cells from the ischemic leg. We found that satellite cells significantly increased smooth muscle migration 2.5 fold compared to media alone using a modified Boyden chamber assay. BrdU staining to assess proliferation showed modest increases in smooth muscle proliferation (1.3 fold change). Finally, to investigate these effects in vivo, we delivered alginate encapsulated satellite cells to mice following the hind limb ischemia procedure. We found that mice that received the encapsulated satellite cells had significantly improved perfusion as measured by Laser Doppler imaging at day 14 post-surgery compared to empty capsules (0.87 ± 0.04 vs 0.68 ± 0.07). These results demonstrate that satellite cells positively influence collateral growth in vivo. We believe that satellite cells play a critical role in collateral vessel formation and are a potential strategy for the treatment of peripheral artery disease.

#31 (morning session)

12 hour interactive health education seminar improves cognition in diverse community dwelling older adults
Hackney ME, Dillard R, Hart A, Wincek R, Jones D, Perkins M

Social, cognitive, and motor function may improve in older adults who participate in educational interventions with small group discussion in which participants recall learned material, relate it to previous knowledge, and form general rules about the information. This single arm, uncontrolled study aimed to determine effects of interactive health
seminars on cognition, psychosocial and motor function in diverse, community dwelling older adults in Atlanta. Forty-seven older adults (20 females; 40% black, 53% white; 7% other; age: M=70.2, SD=9.4; years education M=15.8, SD=2.2; Number of comorbidities: M=3.4, SD=2.4) were assigned to weekly 90-min seminars (over 8 weeks) presented by faculty and medical students. Measures performed before and after the program included: Montreal Cognitive Assessment, Short Test of Functional Health Literacy (STOFHLA), Tower of London (TOL) task, Color Word Interference Task (CWIT), 30s chair stand, gait speed, and the Short Form-12. A satisfaction questionnaire was administered post-program. 39 participants attended at least 6 lessons and improved on CWIT inhibition scaled score (p=.009), and TOL achievement score (p=.001), total rule violations (p=.002). Of participants with marginal or inadequate literacy (n=7), six improved one category on STOFHLA (p<.001). Improved TOL score was moderately (r=.383) correlated with lower health literacy. The program was very well received. This diverse cohort improved on tests of inhibition and planning/organization. Individuals with lower health literacy may have benefitted. Future studies should include individuals with lower health literacy in educational interventions.

#5 (morning session)

Insurance status, progression to stage D heart failure, and mortality in stable outpatients with systolic heart failure
Hedley JS, Velayati A, McCue A, Samman-Tahhan A, Bjork, JB, Swaminath S, Georgiopoulos VV, Phillips V, Kalogeropoulos A

Introduction: Insurance affects access to care. Data on the impact of insurance coverage on disease progression and mortality in patients with heart failure with reduced ejection fraction (HFrEF) are limited.

Methods: We examined 3-year rates of (1) transition to physician-determined Stage D HFrEF (after accounting for competing mortality) and (2) all-cause mortality in 957 stable outpatients receiving care at Emory Healthcare with baseline Stage C HFrEF (ejection fraction ≤40%) not previously on advanced therapies (home inotropes, heart transplant, or mechanical circulatory support [MCS]). Insurance type was classified into Medicare or Medicaid, private, and no insurance.

Results: After a median of 3.1 years (1.9-3.2), 112 patients transitioned to Stage D HFrEF (3-year incidence: 12.3%; annual rate: 4.6%) and 158 died (3-year mortality: 17.7%; annual rate: 6.6%). During follow-up, 42 patients (4.4%) were placed on home inotropes; 21 (2.2%) received MCS; and 7 (0.73%) received heart transplant. Type of insurance was not associated with use of advanced therapies (P=0.67). In models including sociodemographic and clinical characteristics, insurance was not associated with progression to Stage D HFrEF. However, adjusted 3-year mortality was higher among patients with Medicare or Medicaid or no insurance compared to patients with private insurance.

Conclusion: Among Stage C HFrEF patients receiving care in an academic center, rates of transition to Stage D HFrEF were similar regardless of type of insurance. However, despite similar utilization of advanced therapies, mortality was higher among uninsured and Medicare or Medicaid patients.

#49 (afternoon session)

Body fat distribution is associated with oxidative stress

Introduction: Visceral fat is associated with cardiovascular risk factors and an unfavorable metabolic profile. Oxidative stress (OS) is linked to subclinical cardiovascular disease and adverse events. The relationship between fat distribution and OS is unknown.

Hypothesis: Excess visceral (android) fat will be associated with OS.

Methods: Body fat distribution and markers of OS were estimated in 711 healthy volunteers (235 males, 23% African American, mean age 48±11) enrolled in the Emory Georgia Tech Predictive Health study. At 1 year, 498 subjects had repeat testing. Anthropometric, lipid and chemistry panels were obtained. Fat distribution including android and gynoid fat mass were measured by dual energy X-ray absorptiometry (GE Lunar Densitometry, iDXA®). Plasma levels of reduced (cysteine and glutathione) and oxidized (cystine and glutathione disulphide) aminothiols were measured by high performance liquid chromatography to assess OS.

Results: At baseline, body mass indices including BMI, waist circumference, weight/hip ratio, and android and gynoid fat correlated with lower glutathione and higher cysteine levels indicative of higher OS. In a multivariable model adjusting for traditional cardiovascular risk factors and fat distribution, android fat mass remained a negative predictor of glutathione. At one year, the change in android fat negatively correlated with the change in glutathione (r=-0.13, p=0.006).

Conclusions: Body fat distribution, specifically android fat mass, is an independent determinant of OS, measured as lower glutathione levels. Android fat predicts changes in glutathione over time, implying that excess android fat may contribute to development of cardiovascular disease and its adverse events via modulating OS.
Polymerase delta-interacting protein 2 deficiency protects against blood brain barrier permeability in the ischemic brain

Hernandes M, Lassegue B, Cheng L, Yepes M, Griendling KK

Polymerase δ-Interacting Protein 2 (Poldip2) is a multifunctional protein that regulates extracellular matrix via its ability to modify secretion of matrix components and alter matrix metalloproteinase activity. The blood-brain-barrier (BBB) is a dynamic structure assembled by endothelial cells, the basal lamina and perivascular astrocytes, raising the possibility that Poldip2 may be involved in maintaining its structure. We investigated the role of Poldip2 in the barrier function of the BBB in the ischemic brain. Transient middle cerebral artery occlusion (tMCAO) was induced in wild type (WT) and Poldip2+/- mice. Poldip2 protein expression increased in the ischemic brain of WT mice after tMCAO (69±4 vs 20±5 AU) and was predominantly located in astrocytes. Poldip2+/- animals exhibited a significant decrease in Evans blue dye extravasation (25±3 vs 6±2 μM/g), a marker of increased permeability of the BBB, and dramatically improved survival. Poldip2 protein expression was increased in isolated astrocytes following oxygen and glucose deprivation (79±15 vs 27±5 AU), and Poldip2 siRNA prevented cytokine induction under these conditions. As evaluated by RT-PCR, upregulation of cytokine and MMPs mRNA following tMCAO was attenuated in Poldip2+/- mice as follows: MCP-1 (253±34 vs 83±23 AU), IL-6 (134±38 vs 38±10 AU), TNFα (39±12 vs 12±3AU), MMP-2 (19±3 vs 10±1AU), MMP-9 (253±12 vs 13±3AU). The protective effect of Poldip2 depletion on increased permeability of the BBB after ischemia was partially reversed by treatment with TNF-α. Poldip2 is an important regulator of the astrocyte-mediated inflammatory response and BBB disruption in ischemic stroke.

Characterization of plasma cell subsets in systemic lupus erythematosus patients

Hong S, Lee FE, Sanz I

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 SLE, the presence of PCs is deregulated with persistent appearance of increased number of PCs in the circulation. But the properties of these pathogenic PCs still remained to be identified with respect to exact phenotype and longevity. In this study, we found that proportion of CD19-CD138- and CD19-CD138+ PC subsets in total PCs was significantly increased in both active and inactive SLE patients compared to vaccinated healthy controls. Interestingly, Considerable circulating PCs are Ki-67 negative in inactive SLE patients while most post-vaccination PCs are Ki-67 positive. These CD19-PCs from SLE display lower level of HLA-DR and surface Ig.

Moreover, CD19-CD138+ PCs have large vacuoles and have high autophagy activity, features observed in long-lived PCs in bone marrow. Thus, these findings provide a novel insight into characteristic feature of autoreactive PCs and may help to build up strategies to deplete pathogenic plasma cells while leaving the protective PCs intact.

Potential mechanism of the stimulatory effect of low dose Cd in myofibroblast differentiation and lung fibrosis

Hu X, Fernandes J, Jones DP, Go YM

Background: Despite the link of high occupational Cd exposure to lung diseases, the mechanistic toxicity of dietary Cd exposure remains unknown. Low-dose Cd in submicromolar concentration is sufficient to alter cell signaling and redox control mechanism, the critical controllers in the pathogenesis of lung fibrosis. An important step in lung fibrosis is the differentiation of fibroblast to myofibroblast leading to increased contractures and distortion in lung architecture.

Objectives: In this study, we hypothesized that low-dose Cd disturbs nucleus transcriptional regulation and redox signaling, and as a result stimulates fibrosis responses.

Results: Using human fetal lung fibroblasts (HFLF), we found that low-dose Cd stimulated myofibroblast differentiation. Levels of two fibrosis markers synthesized de novo in differentiated myofibroblast, α-smooth-muscle-actin and EDA-containing fibronectin, were significantly increased by 2 and 3 fold, respectively. Cd also stimulated cytoskeletal actin polymerization and stress fibers formation (p < 0.01). To further understand the mechanism, we studied the Cd effects on 45 signal transduction pathways. Cd activated 6 transcription factors (TF) and suppressed 2 TF activity (p < 0.05). SMAD as the mediator of fibrotic response was activated with a 3-fold activity increase in concomitant upregulation of downstream gene expression. In respond to Cd-induced oxidative stress, the redox-regulating thioredoxin-1 (Trx1) translocated from cytoplasm to nucleus. The nucleus-localized Trx1 then activated SMAD to promote profibrotic signaling transduction.

Conclusion: These results suggest that low-dose Cd stimulates lung fibrosis by activating SMAD transcription factor and promotes phenotypic transformation of fibroblast to myofibroblast, providing implications for Cd contributions to lung fibrosis.

The expression of human NHE3 in mouse intestine leads to increased diarrheal symptoms

Jenkin K, He P, Yun CC

Diarrheal disease is a frequent cause of emergency room visits and often results from altered ion transport across the intestine. NHE3, the epithelial Na+ channel, is one of the primary transporters involved in maintaining the osmotic gradient across the intestinal epithelium. In this study, we investigated the role of NHE3 in the pathogenesis of diarrheal symptoms. We found that expression of NHE3 in the mouse intestine was significantly increased in the diarrheal group compared to the control group. This upregulation of NHE3 was associated with increased diarheal symptoms, as evidenced by increased stool frequency and fluid accumulation in the colon.

Conclusion: These findings suggest that the expression of NHE3 plays a critical role in the pathogenesis of diarrheal symptoms, highlighting the importance of targeting NHE3 as a potential therapeutic target for the treatment of diarrheal diseases.
self antigens. Differentiate into antibody secreting cells specific for memory transcriptional program and readily switched memory but differentiated readily into ASC to a level stimulated in vitro they expanded less well switched cytokines IL21, IL10, BAFF, and IL2. When DN2 were stimulated DN2 with the TLR7 agonist R848 and the (ASC). Based on this pattern of gene expression we for differentiation into antibody secreting plasma cells category included several molecules the predispose B cells and effector memory transcription factors. This later reduces CXCR5 expression, and CXCR5- (DN2) are the majority CXCR5 expression, and CXCR5- (DN2) are the majority of gut epithelium by infectious agents. The Na+/H+ Exchanger 3 (NHE3) is responsible for the majority of intestinal electroneutral sodium absorption and is associated with many diarrheal diseases. While mice/rabbits have been used to investigate the mechanisms of diarrhea, they are less prone to develop diarrhea than humans. Recently, we have shown that human NHE3, but not mouse/rabbit NHE3s, interacts with the ubiquitin E3 ligase Nedd4-2. We hypothesize that this property of human NHE3 contributes to the increased severity of diarrhea. To investigate this hypothesis, we generated transgenic mice expressing human NHE3 in the intestine (hNHE3int) and Caco2bb cells transfected with human or rabbit NHE3. The regulation of human and non-human NHE3 in response to forskolin (FSK) or cholera toxin (CTX) was investigated by measuring NHE3 activity and ubiquitination. We found that FSK significantly increased human NHE3 ubiquitination and the extent of inhibition of human NHE3 activity by FSK was greater than rabbit NHE3. Nedd4-2 knockdown blunted the inhibitory effect on human NHE3 but not rabbit. Consistently, inhibition of intestinal NHE3 by FSK was greater in hNHE3int than WT mice. In addition, treatment with CTX led to significantly higher water accumulation in the small intestine of hNHE3int compared to WT mice. These findings demonstrate that human and non-human NHE3s are differentially regulated, suggesting that the characteristics of human NHE3 regulation may contribute to increased diarrhea severity in humans.

#25 (morning session)

Expanded IgD- CD27- B cells in SLE have an effector memory transcriptional program and readily differentiate into antibody secreting cells specific for self antigens.

Jenks SA, Marigora U, Sanz I

B cell homeostasis is perturbed in systemic lupus erythematosus (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- (DN2) are the majority population in SLE patients with expanded DN but not in HCD. Cells with a similar phenotype have been observed in HIV and malaria patients are characterized as non-functional. Given the large expansion of DN2 in SLE patients with severe disease we examined gene expression and antibody production by SLE DN2 to determine if these cells are playing a more active role in SLE pathology. Gene expression demonstrated that DN2 differed from other B cell populations and had a unique profile of cytokine receptors, Toll Like Receptor (TLR) signaling molecules, and effector memory transcription factors. This later category included several molecules the predispose B cells for differentiation into antibody secreting plasma cells (ASC). Based on this pattern of gene expression we stimulated DN2 with the TLR7 agonist R848 and the cytokines IL21, IL10, BAFF, and IL2. When DN2 were stimulated in vitro they expanded less well switched memory but differentiated readily into ASC to a level comparable to switched memory B cells. Furthermore, DN2 ASC produced antibodies specific against several SLE auto-antigens. Overall these experiments demonstrate that DN2 B cells are an important source of pathological antibodies in SLE and a better understanding of DN2 development and regulation may provide novel directions for the treatment of SLE.

#37 (afternoon session)

Relapses versus reinfections: assessing the parasitological and clinical implications using Plasmodium cynomolgi as a model for P. vivax


Plasmodium vivax causes significant morbidity and mortality worldwide and remains a major obstacle to global eradication. One of the obstacles this parasite presents is its liver-stage reservoir comprised of hypnozoites that are capable of reactivating and causing relapses. Relapses are thought to contribute significantly to the prevalence and transmission of P. vivax, but it is unclear if either relapses or reinfections are more responsible for clinical vivax malaria cases. To assess the contribution of relapses and reinfections to clinical vivax malaria, a series of experiments using the rhesus macaque - cynomolgi malaria model were conducted. Relapses did not induce significant clinical alterations, and when minor changes were observed, they resolved without the need for clinical intervention. Homologous reinfections resulted in considerably lower parasite burden and minimal alterations, if any, in clinical parameters, similar to relapses. Interestingly, infection with a heterologous strain of P. cynomolgi did result in significant changes in clinical parameters, although there may have been some clinical protection conferred. Collectively, the data from these experiments suggest that relapses caused by P. vivax parasites that are genetically similar to parasites in primary infections and homologous re-infections likely do not contribute significantly to clinical vivax malaria cases. Contrastingly, infections with genetically dissimilar strains of P. vivax can have pathological consequences, although severity may be less than with the initial infection. Overall, these studies demonstrate that there is much to learn about the clinical consequences of relapses and re-infections and also highlight the complexities of P. vivax infections.

#40 (afternoon session)

Body mass index (BMI) in predicting acute decompensated heart failure outcome

Junpaparp P, Hayek SS, Gupta D

Background: Obesity is associated with incident of heart failure. However, higher BMI is associated with better prognosis in chronic heart failure, known as obesity paradox. We sought to examine the association between BMI and short-term outcomes in patients presenting with acute decompensated heart failure (ADHF), with the
hypothesis that patients with higher BMI will have worse outcomes.

Methods: Medical records of 1,073 patients (29% male, median age 63 years) with ADHF and EF≤40% were reviewed. Clinical characteristics and outcomes (death, readmission for heart failure, and inotrope use) were collected retrospectively. Patients were divided into three subgroups according to BMI: 389, 292 and 392 patients with normal weight (BMI 18.5 to <25), overweight (BMI ≥25 to <30) and obese (BMI ≥30) accordingly.

Results: Patients with higher BMI were younger, and more likely to have hypertension, diabetes, higher albumin and hemoglobin. In-hospital mortality rates were not significantly different between groups (3.1%, 5.1% and 2%, P=0.08), as well as, heart failure re-admission rates at 30-days (22.6%, 20.5% and 21.9%, P=0.81) and 90-days (39.3%, 32.9% and 32.4%, P=0.08, for normal, overweight and obese respectively). There was an increased use of inotropic support among patients with BMI≥30 (HR 1.36, 95%CI 1.01-1.84), which was not significant after adjusting for age, gender and comorbidities.

Conclusion: In this cohort of patients hospitalized with ADHF, higher BMI was not associated with increased in-hospital mortality, use of inotropic support or heart failure readmission. Hypervolemia significantly impacts BMI, and may be a major confounder of the association between BMI and outcomes.

#15 (morning session)

Pregnancy and long-term heart failure risk in women with congenital heart disease


Background: There are limited data on long-term risk for heart failure during or after pregnancy in women with congenital heart disease (CHD).

Methods: We extracted data for women who received CHD related services. Risk for HF was higher among those age 40 or older, but did not differ in female vs. male patients (HR 1.02; 95%CI: 0.74–1.40; P=0.90). However, blacks had significantly higher risk for HF vs. whites (HR: 1.68; 95%CI: 1.18–2.38; P=0.004) in age- and sex-adjusted models.

Conclusions: In a contemporary rToF population of adolescents and adults, HF prevalence increased sharply with age and 5-year incidence was 50%, with higher rates among blacks and those over age 40.

#43 (afternoon session)

Hemolysis reduces HUWE1 through PPARγ downregulation in sickle cell disease-pulmonary hypertension

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

Rationale: Chronic hemolysis in sickle cell disease (SCD) is associated with an increased risk of pulmonary hypertension (PH). We recently observed that Townes
humanized sickle cell (SS) mice developed PH and right ventricular hypertrophy (RVH) and that the peroxisome proliferator-activated receptor gamma (PPARγ) is reduced in SS mouse lungs and in hemin-treated human pulmonary artery endothelial cells (HPAECs).

Objective: We hypothesized that loss of PPARγ reduces levels of HUWE1 and miR-98, leading to increased NF-κB p65 and endothelial dysfunction in SCD-PH. Methods and Results: Levels of the transcription factor NF-κB p65 and endothelial specific markers, such as vascular cell adhesion molecule 1 (VCAM1) and platelet selectin (P-SEL), were increased in the lungs of SS compared to littermate control (AA) mice whereas HUWE1 and miR-98 levels were reduced. In vitro, HPAECs were treated with dimethyl sulfoxide (DMSO) vehicle or hemin (5 μM) for 72 hours. Hemin increased NF-κB p65 and VCAM1 levels and reduced HUWE1 and miR-98 expression. PPARγ overexpression attenuated hemin-induced NF-κB p65 levels. PPARγ knockdown increased NF-κB p65 expression and reduced HUWE1 levels in HPAECs. While knockdown of p65 does not regulate HUWE1 levels, the depletion of HUWE1 increases p65 levels.

Conclusion: Collectively, these findings suggest that PPARγ overexpression may represent a novel therapeutic approach to attenuate these derangements in SCD-PH pathogenesis.

#23 (morning session)

Exaggerated reductions in muscle interstitial pH during exercise in chronic kidney disease
Kang C, Downey R, DaCosta D, Kankam M, Park J

Chronic kidney disease (CKD) patients have exercise intolerance and reduced physical capacity that contribute to increased cardiovascular risk. Muscle interstitial pH decreases during exercise in response to H+ ion extrusion to the extracellular space which is largely buffered by bicarbonate. Reductions in muscle interstitial pH lead to pain, and muscle afferent signaling leading to reflex activation of the sympathetic nervous system during exercise. CKD patients often have overt or occult metabolic acidosis which could lead to decreased capacity to buffer muscle interstitial changes in pH. We hypothesized that CKD patients have exaggerated reductions in muscle interstitial pH during exercise.

We measured muscle interstitial pH and oxygenation (SmO2) using near infrared spectroscopy (NIRS) in 9 CKD patients and 10 healthy controls during 3 minutes of low-intensity rhythmic handgrip exercise (RHG 20%), and high-intensity rhythmic handgrip exercise to fatigue (RHG 40%). We observed that CKD patients had an exaggerated reduction in muscle interstitial pH during high-intensity exercise (p<0.05), but not during low-intensity exercise. There was no difference in SmO2 during low-intensity or high-intensity handgrip exercises between the groups. These findings suggest that CKD patients have exaggerated reductions in muscle interstitial pH during high-intensity exercise that is not mediated by reductions in muscle oxygenation. CKD patients may have lower capacity to buffer pH changes in the muscle interstitium. Exaggerated reductions in muscle interstitial pH may contribute to exercise intolerance in CKD patients by increasing muscle fatigue, pain, and reflex activation of sympathetic nerve activity which could contribute to abnormal hemodynamic responses during exercise.

#62 (morning session)

Chronic kidney disease, life-space restriction, and mortality in the UAB study of aging
Kappel JD, Johnson TM, Bowling CB

Background: Chronic kidney disease (CKD) prognosis relies on estimated glomerular filtration rate (eGFR). The life-space mobility assessment is a novel measure that quantifies the distance, frequency, and independence achieved as older adults move through their environment. Although life-space restriction (LSR) has been shown to be associated with mortality, its prognostic significance has yet to be examined in older adults with CKD.

Methods: Using a subset (n=400) of the University of Alabama-Birmingham Study of Aging, we investigated the joint effects of CKD, defined by eGFR<60 ml/min/1.73m², and LSR, defined as composite life-space score<60, on all-cause mortality using Cox proportional hazards regression adjusting for sociodemographics and medical comorbidities.

Results: Overall, 50% of participants had CKD and 45% had LSR. Mortality rates (per 1,000 person-years) were 31.3, 38.6, 87.4, and 80.0 among those with No CKD/No LSR, CKD/No LSR, No CKD/LSR, and CKD/LSR. Compared to participants with neither exposure (No CKD/No LSR), hazard ratios (HR; 95% confidence intervals) for mortality were 1.07 (0.52-2.19), 2.11 (1.06-4.17), and 1.94 (0.97-3.90) for the CKD/No LSR, No CKD/LSR, and CKD/LSR groups. Using a CKD cut-point of eGFR<45 ml/min/1.73m², multivariable adjusted HRs were 1.51 (0.63-3.60), 1.86 (1.03-3.35) and 3.26 (1.64-6.50) respectively. After stratification of the sample by CKD status, HRs for the association between LSR and mortality, adjusted as above, were 1.79 (0.89-3.64) in those with CKD and 2.48 (1.13-5.43) in those without CKD.

Conclusions: Restricted life-space is associated with increased mortality risk and may provide additional prognostic information to guide CKD management beyond that offered by eGFR.
Neighborhood income rather than food access is associated with adverse cardiovascular outcomes in food deserts


Introduction: Environmental characteristics and limited access to healthy food have been associated with cardiovascular risk factors. We evaluated the impact of living in food deserts on cardiovascular events and whether neighborhood income or food access is driving the health effect of food deserts.

Methods: Subjects undergoing cardiac catheterization and recruited into the Emory Cardiovascular Biobank had their zip codes entered into the Food Deserts Atlas that specifies food deserts as combined low food access and low income areas. Cox proportional hazard models were used to analyze the association of these area characteristics with all-cause mortality and myocardial infarction (MI).

Results: Of the 5240 patients (age 63±12, 64% male) enrolled, 1056 (24.1%) were living in low income areas, 1723 (32.9%) in low food access areas, and 1056 (20.2%) in food deserts. During a median follow-up of 3.2 years, 988 (18.9%) patients died or developed a MI. After adjustment for cardiovascular risk factors patients within food deserts had higher risk of adverse events with hazard ratio (HR) of 1.28. (95% CI 1.04 – 1.58), p=0.018. However, when compared to subjects in high income and good food access areas, those with high income and low access had similar outcomes HR 0.99 (CI 0.82-1.20). Moreover, subjects within low income neighborhoods with good food access had similar outcomes to those in food deserts HR 0.96 (CI 0.78-1.16).

Conclusion: Although living in food deserts is associated with a higher risk of death and MI, its impact is mainly due to area income rather than food access.

Life-space mobility decline in peripheral arterial disease

*Khakharia A, Shipra A, Bowling CB*

Introduction: Symptomatic Peripheral arterial disease (PAD) impairs walking, but data on the impact of PAD on community mobility are limited. Life-space-mobility (LSM) measures the distance, frequency, and assistance needed as older adults move through geographic areas extending from their bedroom (LSM=0) to beyond their town (LSM=120). We evaluated the association of PAD with longitudinal LSM trajectory.

Methods: Participants were part of the University of Alabama at Birmingham Study-of-Aging, a longitudinal study of community-dwelling older adults. We limited our analysis to those who survived at least 6 months (n=981). PAD was based on self-report with verification by physician/hospital records. Our primary outcome was LSM assessed every six-months. A mixed effects model was used to determine the association between PAD and life-space mobility trajectory over a median 7.9 years of follow-up.

Results: Participants had a mean age of 75.7 (SD=6.7), 50.5% were female and 50.4% were African American. The prevalence of PAD was 10.1%. In a multivariable adjusted mixed effects model, participants with PAD had a more rapid decline in LSM by -1.1 (95% CI -1.9,-0.24) points per year compared to those without PAD. At five year follow-up, model adjusted mean LSM (95% CI) was 48.1 (43.5, 52.7) and 52.4 (50.9–53.8), among those with and without PAD, respectively, corresponding to a restriction in independent LSM at the level of one’s neighborhood.

Conclusions: The presence of PAD is associated with significant decline in LSM among community-dwelling older adults. Further study is needed into the impact of PAD associated life-space limitations on social/functional decline.

Introduction: Right heart failure (RHF) following implantation of left ventricular assist device (LVAD) remains an unresolved concern. Previous studies focused on early RHF, which occurs immediately after the implantation. However, little is known about the risk factors, incidence, and outcomes of late-onset RHF.

Methods: A total of 110 patients who underwent LVAD implantation at Emory University in 2012-2015 were reviewed. Pre-operative cardiovascular risk factors and echocardiographic and hemodynamic parameters were compared between those who developed early RHF, late RHF, and no RHF. Early RHF was defined as any case which required >14 days of post-operative inotropes. Late RHF was defined as any case without early RHF which eventually required inotropes after the initial discharge. Univariate Cox regression was used to evaluate the association between pre-operative risk factors and late RHF.

Results: Late RHF occurred in 15 patients (14%), and early RHF occurred in 16 patients (15%). The median onset of late RHF was 159 days from the surgery (range 22–1,129 days). Late RHF was associated with an increased risk of mortality at 2-year follow-up (HR 2.39, 95% CI [1.04–5.49], P=0.041). Higher pre-operative serum creatinine was significantly associated with a greater risk of late RHF (HR=1.24 per 0.05 mg/dL, 95% CI [1.04–1.48], P=0.014). Other demographic, echocardiographic, and hemodynamic parameters were not significantly associated with late RHF.

Conclusions: Late RHF is a common morbidity after LVAD implantation and is associated with great mortality. Poor pre-operative renal function, estimated by elevated creatinine, is a risk factor for late RHF.

Cystic fibrosis impairs the protective effects of insulin in the airway Molina, SA, Vance R, McCarty NA, Koval M

Patients with cystic fibrosis (CF) live with chronic airway infections. An increased rate of decline in lung function correlates with diagnosis of CF-related diabetes (CFRD). Since the lung function of patients diagnosed with CFRD declines at an accelerated rate and since insulin controls glucose metabolism, the effect of insulin on CF airway epithelia was investigated. We determined whether airway epithelia have functional insulin receptors that could regulate both glucose uptake and paracellular flux and whether these responses are impaired in CF. Human airway epithelial cells matured at air-liquid interface were characterized by qPCR, immunoblot, immunofluorescence, paracellular flux, and 2-[3H]-deoxyglucose uptake assays. PKB/Akt signaling and CFTR activity were analyzed by pharmacological and immunoblot assays. Insulin increased glucose uptake and reduced paracellular flux in normal primary human airway epithelial cells. Insulin-stimulated glucose uptake correlated with translocation of Glut4 to the apical membrane. Human airway cells expressing F508del-CFTR treated with insulin did not increase glucose uptake and increased the rate of glucose flux. Insulin stimulated phosphorylation of Akt in normal airway cells, but not in CF.
Airway cells. Inhibition of either PI3K or CFTR in normal human airway cells mimicked the defects observed in the human CF airway cells. Therefore, the “airway glucose barrier” is dysfunctional in human CF airway epithelial cells and may contribute to nutrient leak into the airway, a potential food source for microbes. Since Akt activation by insulin is impaired in human airway cells expressing F508del-CFTR, an insulin-independent approach may be needed to treat CFRD.

#41 (morning session)

**Association of zika virus persistence and CD8+ T cell dysfunction during acute infection**


**Background:** To facilitate Zika virus (ZIKV) vaccine, therapeutic, and diagnostic development we studied immune responses and viral persistence in acute and convalescent patients.

**Method:** Three acutely viremic US travelers (including 2 pregnant and 1 immunocompromised [IC]) and 7 convalescent patients provided whole blood. Samples were phenotyped for CD27+CD38+ plasmablasts or HLA-DR+CD38+ activated T cells. Virus-specific plasmablasts and memory B cells (ELISpot), Intracellular cytokine staining of T cells (ICS), neutralizing antibodies (NAb), and ZIKV RNA (qRT-PCR) were quantitated.

**Result:** Two pregnant patients had ZIKV persistently detectable in plasma through 45 and 48 days post-symptom onset respectively. 10-30% of CD8 T cells and 3-4% of CD4 T cells were activated within the first week of symptom onset. ASC peaked on D7 at 19% of total B cells and were ZIKV- and DENV-specific. High titers of NAb were also detected. ZIKV-specific CD4+ T cells produced cytokines upon stimulation with ZIKV peptides. CD8+ T cells, although highly activated, were unable to produce cytokines. A similar pattern was observed in an IC patient. In contrast, in 5 of 8 convalescent healthy, non-pregnant patients with resolved ZIKV infections, CD8+ T cells produced cytokines after ZIKV peptide stimulation on days 28-126.

**Conclusion:** Acute ZIKV infections produced strong CD8+ T cell activation, NAb responses and more modest CD4+ T cell activation. Despite these robust immune responses and cytokine-producing virus-specific CD4+ T cells, viremia persisted long past the typical 1-week window in 2 of 3 acute patients (2 pregnant women) and was associated with CD8+ T cell dysfunction.

#56 (afternoon session)

**Osteopontin isoform-induced neovascularization is mediated by effects on macrophage cell migration and survival**

Lee GS, Caroti CM, Salazar H, Joseph G, Weiss D, Taylor WR, and Lyle AN

Coronary and peripheral artery diseases result in vessel occlusion and ischemia, initiating collateral formation to restore blood flow. We previously demonstrated that osteopontin (OPN), a matricellular cytokine, is critical to ischemia-induced neovascularization. Unlike rodents, humans express 3 OPN isoforms (a, b, and c); however, how OPN isoforms affect collateral formation and cell migration remain undefined. To assess if OPN isoforms affect collateral formation, OPN-/- mice underwent hindlimb ischemia surgery and received lentivirus particles expressing OPNa, OPNb or OPNc by IM injection. OPNa and OPNc improved perfusion, as measured by laser Doppler perfusion imaging. These effects were not due to isoform expression differences, as confirmed by ELISA. We hypothesized that OPN isoforms have divergent effects on collateral formation due to differential effects on macrophage migration, survival, and/or polarization. We found no isoform-dependent differences in macrophage polarization, but OPNa and OPNc increased microphage infiltration in vivo. To determine if OPN isoforms promote microphage migration in vitro, we used a modified Boyden chamber assay. OPNc increased microphage migration and proved more potent than OPNa, OPNb or MCP-1. In addition, OPN-/- microphage were serum-deprived to induce apoptosis and were treated with OPNa, OPNb or OPNc in vitro. All OPN isoforms increased microphage survival 3-fold, as assessed by FITC-annexin V and propidium iodide staining using FACS. In conclusion, OPN isoforms differentially affect collateral formation and cell migration due to differential effects on microphage survival and have divergent effects on microphage migration, supporting that OPN isoforms may be novel therapeutic targets to improve neovascularization in patients with obstructive artery disease.

#8 (afternoon session)

**Global longitudinal strain recovery after transcatheter aortic valve replacement: restoring of flow, gradient and mechanics**


**Aim:** Global longitudinal strain (GLS) has incremental value in assessing left ventricular function in severe aortic stenosis and is related to clinical outcome after transcatheter aortic valve replacement (TAVR). We sought to identify relevant factors for positive and negative GLS change post TAVR.

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**Aim:** Global longitudinal strain (GLS) has incremental value in assessing left ventricular function in severe aortic stenosis and is related to clinical outcome after transcatheter aortic valve replacement (TAVR). We sought to identify relevant factors for positive and negative GLS change post TAVR.
Methods and Results: We analyzed 123 patients with severe aortic stenosis who underwent TAVR. 55 had reduced baseline left ventricular ejection fraction (LVEF ≤50%, rEF), and 68 had preserved LVEF (LVEF >50%, pEF). After 12 months, GLS improved by 36% in rEF patients (-9.7±2.9% vs -13.2±4.0%, p=0.0001) and 17% in pEF patients (-15.0±4.2% vs -16.8±4.7%, p=0.001). GLS declined in 30 patients (24%) by more than an absolute value of 10% after 12 months. Most of these patients did not show GLS recovery during extended follow-up. Baseline GLS better than -10.2% and stroke volume index (SVi) >28.5 ml/m2 predicted more than 10% GLS improvement in rEF patients (AUC 0.81 and 0.62, sensitivity 78% and 81%, specificity 79% and 43%). GLS better than -15.0% and mean aortic pressure gradient >57mmHg predicted greater than 10% GLS improvement in pEF patients (AUC 0.76 and 0.66, sensitivity 64% and 39%, specificity 72% and 91%). Post-TAVR SVi ≤39.7 ml/m2 was associated with greater than 10% GLS deterioration.

Conclusion: Baseline GLS is the strongest predictor of GLS improvement after TAVR for severe aortic stenosis. Baseline SVi and MPG also predict improvement in GLS after TAVR in rEF and pEF groups respectively. Persistently depressed SVi is associated with worsened GLS.

Probiotics, which are defined as viable microorganisms that confer a health benefit, prevent ovariectomy (ovx) induced bone loss, but their mechanism of action remains unknown. 10-week-old mice were ovx or sham operated and treated for 4 weeks with vehicle or the probiotics L. rhamnosus GG (LGG) and VSL#3. Control treatments included vehicle, a strain of E. coli, and LGG pili mutant (LGGM), a strain lacking epithelial adhesion. In a second experiment, LGG and VSL#3 were administered to intact 16 week old mice experience severe polyuria and have trouble reabsorbing water back into the body. The protein responsible for the kidney's inability to respond to vasopressin. NDI patients

Liwang JK, Sands JM, Klein JD, Wang Y

Probiotics, which are defined as viable microorganisms that confer a health benefit, prevent ovariectomy (ovx) induced bone loss, but their mechanism of action remains unknown. 10-week-old mice were ovx or sham operated and treated for 4 weeks with vehicle or the probiotics L. rhamnosus GG (LGG) and VSL#3. Control treatments included vehicle, a strain of E. coli, and LGG pili mutant (LGGM), a strain lacking epithelial adhesion. In a second experiment, LGG and VSL#3 were administered to intact 16 week old mice for 8 weeks. µCT measurements revealed that LGG or VSL#3 completely prevented the increase in bone resorption and the loss of femoral bone volume (BV/TV) induced by ovx. LGGM was only partially effective and E. Coli did not prevent bone loss. Moreover, LGG or VSL#3 induced a significant increase in BV/TV when fed to intact mice, while E. Coli and LGGM did not. Ovx increases gut permeability to cause enhanced production of the inflammatory/osteoclastogenic factors RANKL, TNF and IL-17 in the intestine and the bone marrow. Treatment with LGG and VSL#3 normalized epithelial tight junction proteins thus preventing the detrimental effects of ovx on gut permeability and cytokine production in the gut and the bone marrow. Mechanistic studies of the bone anabolic activity of probiotics in intact mice revealed that LGG and VSL#3 increase stromal cell commitment to the osteoblastic lineage and osteoblast differentiation by activating Wnt signaling. In summary, probiotics supplementation may thus represent an effective therapeutic strategy for the prevention and treatment of postmenopausal bone loss.

#21 (morning session)

Dialysis facility providers perceptions of racial, gender, and age disparities in renal transplantation

Medical providers’ attitudes can greatly influence patient care and outcomes and greater focus is needed regarding provider perceptions of renal transplant disparities. This study assesses southeastern (Georgia, North Carolina, and South Carolina) dialysis facility (N = 509) staff philosophies regarding renal transplantation. Analysis of 2013 data was conducted on 3 open ended questions that asked dialysis staff to discuss their experiences and observations regarding renal transplant disparities among African Americans, women, and elderly patient populations. Study results suggest that dialysis facility staff viewed financial barriers as the main contributor to transplant disparities for African Americans patients, familial responsibility as a barrier for women, and fear of being too old for elderly ESRD patients. However, there was no attribution to provider contribution to renal transplant inequalities. Results also suggest that a small percentage of dialysis staff were unaware of existing disparities. Dialysis facilities should be encouraged to place greater attention on existing racial, gender, and age gaps in renal transplantation and the role staff may play in these inequities via education and cultural competence training.

#23 (afternoon session)

The effects of PKC and AMPK on water reabsorption in rat inner medullary collecting duct
Liwang JK, Sands JM, Klein JD, Wang Y

Nephrogenic Diabetes Insipidus (NDI) is caused by the kidney's inability to respond to vasopressin. NDI patients experience severe polyuria and have trouble reabsorbing water back into the body. The protein responsible for the reabsorption of water is aquaporin-2 (AQP2), which is located on the apical surface of the inner-medullary (IM) collecting duct. Recent studies suggest that protein kinase C (PKC) and adenosine monophosphate-activated protein kinase (AMPK) phosphorylate and activate AQP2; however, it is unknown if they stimulate through parallel signaling pathways or if they are interdependent. Our hypothesis is that PKC and AMPK are able to stimulate AQP2 independently and additively. To prove this, we examined the expression levels of AQP2 and AMPK using Western blot analysis. Rat IM tissues were treated with chelerythrine (PKC inhibitor,10µM), Compound C (AMPK inhibitor, 12.5µM), phorbol dibutyrate (PKC activator, 4µM), Metformin (AMPK activator, 4µM), and H-89 (PKA inhibitor, 5µM) at 37°C for 30 minutes. The antibodies used to
Hydrogen sulfide protects from Pth induced bone loss by increasing WNT10B production by T cells

Hydrogen sulfide (H2S) is a gasotransmitter that has recently been implicated in physiologic mesenchymal stem cell renewal and osteogenic differentiation, as well as acquisition of bone during postnatal growth. Treatment with H2S have been shown to prevent ovariectomy induced bone loss and alveolar bone loss. In this study we have investigated the capacity of the H2S donor GYY4137 to prevent the bone loss induced in mice by continuous PTH (cPTH) treatment, a model of primary hyperparathyroidism. 16 week old female mice were infused with hPTH1-34 (80 μg/kg/day) by osmotic pumps for 2 weeks and injected IP with vehicle or the H2S-donor GYY (1mg/mouse/day). GYY treatment completely prevented the loss of trabecular and cortical bone induced by cPTH by stimulating bone formation. Mechanistic studies revealed that GYY increased osteoblastogenesis and osteoblast life span by activating Wnt signaling in bone marrow (BM) stromal cells. Wnt signaling activation was due to increased production of the osteogenic Wnt ligands Wnt10b by BM T cells. In summary, GYY is an H2S donor that potently stimulates bone formation by activating Wnt signaling in osteoblastic cells. Since treatment with GYY protects against cPTH induced bone loss, our data provide a proof of principle that GYY donors may represent a new therapeutic approach for induced bone loss.

Conclusion: PKC and AMPK work independently to stimulate AQP2. However, when activated together, PKC and AMPK are not additive in stimulating AQP2 to increase water reabsorption. Understanding the regulation of AQP2 will help us understand how urine-concentrating defects occur in NDI and may suggest novel treatment strategies.

#52 (morning session)

Hydrogen sulfide protects from Pth induced bone loss by increasing WNT10B production by T cells


We previously determined that alcohol exposure induced TGFβ1 in the lung and lung fibroblasts. Further, treatment with sulforaphane attenuated TGFβ1 expression in lung fibroblasts. However, the mechanism by which alcohol and sulforaphane mediate TGFβ1 is unknown. Several non-coding RNAs have been shown to regulate gene expression through suppression of gene transcription leading to down-regulation of a target gene. MicroRNA-21 (miR-21) has been shown to target Smad7, a TGFβ1 inhibitor, and is associated with lung fibrosis. We hypothesized that alcohol induced expression of miR-21, leads to suppression of Smad7 and up-regulation of TGFβ1 expression in lung fibroblasts. In parallel, sulforaphane attenuates alcohol-induced TGFβ1 expression through suppression of miR-21 expression. Mouse primary lung fibroblasts were cultured ± alcohol (60 mM) ± sulforaphane (5 M). MicroRNA-21 expression was analyzed at 24 and 48 hours. In parallel, Smad7 gene and protein expression were analyzed at 24 and 48 hours, respectively. Alcohol exposure increased miR-21 expression in lung fibroblasts at 24 and 48 hours. Further, alcohol attenuated both Smad7 gene and protein expression in lung fibroblasts. Treatment with sulforaphane attenuated miR-21 expression and increased Smad7 gene expression as compared to the alcohol-treated group. Alcohol induces TGFβ1 through induction of miR-21 which leads to suppression of TGFβ1 inhibitor, Smad7. Our data suggests that treatment with sulforaphane might attenuate TGFβ1 through suppression of miR-21 and an increase in Smad7 expression. These findings provide new insight into how alcohol promotes fibrotic disrepair and treatment with sulforaphane could prevent the effect of alcohol on lung repair following acute injury.

#2 (afternoon session)

Predictors and outcomes of improved left ventricular ejection fraction in outpatients with heart failure and reduced ejection fraction

McCue AM, Samman-Tahhan A, Hedley JS, Bjork JB, Gupta D, Smith AL, Georgiopoulou VV, Kalogeropoulos AP

Introduction: Limited data are available on factors associated with improvement/recovery of left ventricular ejection fraction (LVEF) in outpatients with heart failure (HF) and reduced (<40%) LVEF (HFrEF) and the impact of improvement on outcomes.

Hypothesis: We hypothesized that clinical characteristics can predict improvement of LVEF (to >40%) in HFrEF outpatients and that this improvement leads to lower risk for subsequent events.

Methods: We evaluated 492 patients with HFrEF who received outpatient care in our institution from 01/01/12 to 03/31/12 (inception period) for subsequent echocardiographic LVEF assessments and outcomes (death, HF admission) over the next 2 years.

Results Among 1-year survivors (N=468; 95.1%), 272 had repeat echocardiograms at 1 year (58.1%). Of those, 44/272 (16.2%) had improved LVEF (mean change,
Internally guided lower limb movement recruits compensatory cerebellar activity in Parkinson’s disease


Externally guided (EG) and internally guided (IG) movements recruit parallel neural circuits, in which cortical motor neurons interact with either the cerebellum or striatum via distinct thalamic nuclei. EG movements rely more heavily on the cerebello-thalamo-cortical circuit, whereas IG movements rely on the striato-thalamocortical circuit. Because Parkinson’s disease (PD) involves striatal dysfunction, individuals with PD have difficulty generating IG movements. We hypothesized that during IG lower limb movements, individuals with PD employ a compensatory strategy favoring the cerebellum over the striatum. In the current study, 22 adults with mild-moderate idiopathic PD (age M=68.6, SD=9.7; Hoehn & Yahr M=2.3, SD=0.6), while off anti-PD medications, and 19 age-matched controls without PD (age M=65.6, SD=9.7) performed EG and IG rhythmic foot tapping tasks, counterbalanced in a block design, functional magnetic resonance imaging paradigm. Prior to scanning, participants learned a repetitive right foot tapping pattern with .5 s and 1 s intervals. An assistant paced EG trials by tapping participants’ ipsilateral 3rd metacarpal. IG trials were participant-paced. Neural activation was compared between tasks (EG vs. IG) and groups (PD vs. non-PD). Both groups employed the cerebellar and striatal motor circuits described above, but the PD group demonstrated less activation in the striatum and motor cortex than the non-PD group. A task (EG vs. IG) by group (PD vs. non-PD) interaction was observed in the cerebellum, supporting the hypothesis that the dysfunctional striatum is assisted by the less affected cerebellum to accomplish foot movement. These findings will contribute to investigations into mechanisms of effective rehabilitation.
this retrospective case-controlled study. An adult control group was matched per case on ASGE procedural complexity, endoscopist, year performed, and gender.

Results: Among 214 ERCPs performed in 51 pediatric patients (107 procedures) and in 91 ASGE grade-matched adult controls (107 procedures), 57.5% were performed on a native papilla and 29% were complex procedure (ASGE grade 3 and 4). The primary indications were biliary obstruction (52.3%) and recurrent pancreatitis (34.6%). There was no statistically significant difference in the technical success rate, clinical success rate, or complication rate between pediatric ERCP and control group. The main complication was post-ERCP pancreatitis (2.8%). There was no significant difference in cannulation device, fluoroscopy time, procedural duration, length of hospitalization, or number of repeat procedures. General anesthesia and post-procedural admission rates were higher in pediatric group (OR 4.69, 95%CI 2.63-8.38; p<0.0001 and OR 3.3, 95%CI 1.5-7.1; p=0.002, respectively). The outcomes remained the same in subgroup analysis of complex procedures and index procedures.

Conclusion: ERCP in a pediatric population is equally safe and effective relative to ASGE complexity-matched ERCP in adults when performed by adult gastroenterologists. Pediatric patients are more likely to require general anesthesia and admission post-procedure.

#34 (morning session)

**Gastric peroral endoscopic pyloromyotomy (G-POEM) as a salvage therapy for refractory gastroparesis: a case series of different subtypes**

Mekaroonkamol P, Li L, Dacha S, Xu Y, Keilin S, Willingham FF, and Cai Q

Gastroparesis is a debilitating disorder with limited therapeutic options. Gastric Peroral Endoscopic Pyloromyotomy (G-POEM) is a novel endoscopic technique for an incisionless pyloroplasty. Existing data on its procedural techniques, safety, and efficacy are sparse. This study is a retrospective review of G-POEM procedures using selective circular myotomy with intention to preserve longitudinal muscle as a salvage therapy for refractory cases in 3 different subtypes of gastroparesis. A 75-year-old male with post-surgical gastroparesis presented with worsening post-prandial symptoms requiring total parenteral nutrition (TPN). 5-month after G-POEM, his gastric emptying scintigraphy (GES) normalized from 75% pre-procedure to 4% at 4-hour. His Gastroparesis cardinal symptoms index (GCSI) improved from 28 to 7. A 28-year-old male with post-surgical gastroparesis underwent a G-POEM procedure. At 1-month follow up, his GCSI improved from 23 to 6. Her GES improved from 95% to 75% residual at 2-hour. G-POEM is an effective less-invasive treatment option in patients with different subtypes of refractory gastroparesis. Our cases are the firsts to show success of G-POEM in post-infectious gastroparesis and in elderly male patient. There was no complication observed. More data is needed to determine which subgroup of patients would benefit most from this novel procedure.

#64 (afternoon session)

**miR-155 a possible link between angiotensin II receptor type 1 and ETS1-mediated vascular dysfunction in acute oscillatory shear stress (OSS) setting**

Mohamed IN, Thomas S, Rooney K, Sutliff R, Willet N and Searles CD

Introduction: Disturbed blood flow & shear stress forces play an integral role in dictating vascular inflammation & development of atherosclerosis. Previously, our group has identified microRNA-155 (miR-155) as a key shear-sensitive miRNA in vasculature and in vitro. Hypothesis: Acute induction of low magnitude oscillatory shear stress (OSS) leads to vascular dysfunction via dysregulation of miR-155.

Methods: 12-week old C57B/6J (WT) and Angiotensin II receptor type 1a-deficient (AT1Ra-/-) mice were subjected to abdominal aortic coarctation (AAC) for 3 days. Segments exposed to OSS were compared to unidirectional shear stress (USS) segments in the same aorta as well as aortic segments from sham mice.

Results: In WT mice, miR-155 levels in OSS segments from AAC mice were down regulated compared with corresponding segments of sham mice. Down regulation of miR-155 was associated with upregulation of its validated pro-inflammatory targets: AT1Ra, ETS1 & downstream effectors, MCP-1, VCAM-1, and MMP9. In parallel, OSS segments from AAC mice showed increased extravasation of Evans-blue dye compared with USS. These changes were associated with increased reactive oxygen species (ROS) levels, impaired endothelial dependent relaxation & differential contractile response to phenylephrine. In contrast, AT1Ra-/- mice showed upregulation of miR-155 in OSS segments and abrogation of the acute OSS effects on inflammation and ROS levels (n=3-6, P<0.05).

Conclusions: Acute OSS results in AT1Ra-mediated activation of the ETS1 pathway and dysregulation of its upstream inhibitor, miR-155. These results suggest miR-155 as a potential switch that connects between OSS and vascular dysfunction by modulation of the AT1Ra-ETS1 pathway.
Red blood cell derived microparticles modulate endothelial cell phenotype through regulation of heme oxygenase-1
Mohandas AN, Mitchell AJ, Gray WD, Thomas SA, Rooney K, Searles CD

Background: Red blood cells are known to generate microparticles, termed red cell microparticles (RMPs), which are among the most abundant MPs in human circulation and are known to accumulate during RBC storage. Microparticles are known to transfer proteins and RNA. We hypothesized that RMPs are internalized by human aortic endothelial cells (HAECs), transfer RNA and protein cargo, and alter the response of cells to inflammatory stimuli through modulation of heme oxygenase-1 (HO-1).

Methods: RMPs were isolated from stored human RBC transfusion units by centrifugation. RMPs were labeled with a fluorescent membrane dye (PKH-26), and incubated with HAECs for 24 hours at a concentration of 6 x 10^6 MPs/mL. Internalization of RMPs by HAECs was assessed by confocal microscopy and flow cytometry. HO-1 levels were determined by western blot analysis. ROS levels in endothelial cells (ECs) were determined by flow cytometry using the ROSstar 650 probe.

Results: Our studies confirm cellular internalization of RMPs by HAECs. RMP treatment reduced EC levels of ROS in the presence of TBHP (0.78 fold, p<0.05). Hemoglobin was detected in RMP-treated cells but not in untreated controls. Heme oxygenase-1 was upregulated at both the mRNA (2.2-fold, p<0.05) and protein level (3-fold, p<0.05).

Conclusion: RMPs transfer hemoglobin to HAECs in vitro, thereby activating the heme oxygenase pathway, which may account for the observed antioxidative effects of RMPs on HAECs. These studies raise questions regarding the possibility of RMPs mediated communication between RBCs and the vascular endothelium, as well as the potential effects of RMPs in transfused blood.

Glial cell line derived neurotrophic factor enhances hepatocyte mitochondrial fatty acid oxidation and survival
Mwangi SM, Kailar R, Kleinhenz JM, Hart CM, Srinivasan S

Aims: We recently showed that glial cell line derived neurotrophic factor (GDNF) is protective against high fat diet -induced hepatic steatosis in mice, however, the mechanisms involved are not fully understood. In this study we investigated the role of GDNF in modulating hepatocyte mitochondrial function, fatty acid oxidation and cell survival.

Methods: HepG2 cells were cultured for six days in medium supplemented with or without GDNF (200 ng/ml) and palmitate (0.1 mM) and mitochondrial function assessed by measuring oxygen consumption rates. Cell survival was assessed in cells cultured for 24-72h in medium supplemented with GDNF and palmitate (0-0.25 mM).

Results: HepG2 cells cultured for 6 days in medium supplemented with GDNF alone had higher basal and maximal mitochondrial respiration than cells cultured in vehicle alone when assessed both in the absence (basal: 132.6 ± 2.5 vs. 74.53 ± 1.6 pmol O2/min; P=0.0001; maximal: 183.8 ± 7.7 vs. 103.2 ± 4.4 pmol O2/min; P=0.0001) and presence of palmitate (basal: 229.1 ± 5.8 vs 179.1 ± 9.9 pmol O2/min; P=0.0015). Similarly, HepG2 cells cultured for 6 days in the presence of both GDNF and palmitate had higher basal respiration than cells cultured in palmitate alone. Additionally, GDNF enhanced cell survival both in the presence and absence of palmitate.

Conclusions: We demonstrate a novel role for GDNF in the regulation of hepatocyte mitochondrial function and survival. Our studies show that GDNF could be a useful tool for enhancing hepatocyte fatty acid oxidation and in protecting against hepatic steatosis and lipotoxicity.

Risk factors and regional differences in hospitalization among individuals waitlisted for kidney transplant
Newman KL, Adams AB, Zhang R, Lynch RJ, Pastan SO, Patzer RE
Background: For individuals waitlisted for a deceased-donor kidney, hospitalization is associated with a lower likelihood of transplantation and poor post-transplant outcomes. Hospitalization also adds to higher healthcare costs. However, risk factors for hospitalization among individuals waitlisted for kidney transplantation have not been investigated.

Methods: We used United States Renal Data System Medicare-linked data on patients waitlisted between 2005 and 2009 with continuous enrollment in Medicare Parts A & B (n=27,735) to examine the association between annual hospitalization rate and a variety of demographic, clinical, and social factors. We used multivariable ordinal logistic regression to estimate odds ratios (OR).

Results: Nationally, factors associated with significantly increased hospitalization rates among waitlisted individuals include black race, female sex, body mass index<18.5, panel reactive antibody>0, public insurance at ESRD diagnosis, years on dialysis prior to waitlisting, ESRD/CKD caused by diabetes, and having a history of tobacco use (all p<0.05). Factors associated with significantly lower hospitalization rates include Asian race and history of prior transplant (p=0.007 and p=0.016, respectively). For dialysis-dependent individuals, those with arteriovenous fistulas were significantly less likely than individuals with catheters or grafts to be hospitalized (OR=0.74 and 0.79, respectively, both p<0.001). There was also regional variation in hospitalization rates, with the lowest rates in the northwest (UNOS region 6) and the highest rates in the mid-Atlantic (region 2).

Conclusion: Individual-level variables and dialysis access type are significantly associated with hospitalization while waitlisted. However, there are also regional differences in hospitalization, suggesting that system-level factors may also contribute.

#24 (morning session)

Genotypic resistance mutation pattern of integrase strand transfer (INST) gene in HIV-infected patients on INST inhibitor-containing regimen

Nguyen ML, Anderson AL

Background: The first integrase strand transfer inhibitor (INSTI) was approved by the FDA in 2007 for use in HIV-infected patients. Since then, INSTI has become prominent in the field of antiretrovirals, with all 3 drugs in this class being recommended for use in antiretroviral-naive HIV individuals. We are reviewing mutations patterns of individuals who failed antiretrovirals that contained an INSTI.

Methods: A retrospective review of INSTI genotypic resistance electronic records was performed for July 1,2015 to June 30,2016. Medical records of identified individuals were reviewed.

Results: There were 647 INSTIR genotyping ordered during the one-year period, of which 61% was credited for various reasons. Among the 259 resulted INSTI genotypes, 95% had no resistance INSTI mutations and 5% had predicted or probable resistance, among which 3 had resistance to dolutegravir, with mutations at locations 66,92 and 155 being the common locations. All individuals who developed predicted or probable resistance to dolutegravir had mutation at 148 in addition to other mutations. All INSTI-R individuals had prior exposure to antiretrovirals.

Conclusion: Reviewing mutation pattern among INSTI users will teach about mechanisms of resistance. Providers should be vigilant to inquire about prior ART use and monitor for adherence to identify suspected INSTI-R to avoid accumulation of resistance mutations that will result in loss of all drugs efficacy in entire INSTI class.

#9 (morning session)

Relationship between peripheral vascular responses with mental stress and mental stress-induced myocardial ischemia


Background: Mental stress-induced myocardial ischemia (MSIMI) in patients with CAD is unrelated to its severity and is associated with adverse cardiovascular outcomes. The impact of vascular function and its response to mental stress (MS) on the development of MSIMI remains unclear. We measured endothelial function and arterial stiffness, and their change with MS, with the hypothesis that abnormalities in the vascular functional responses will contribute to MSIMI.

Methods: Patients with stable CAD underwent 99mTc sestamibi myocardial perfusion imaging during MS testing using a public speaking stressor. MSIMI was defined as impaired myocardial perfusion using a 17-segment model. Endothelial function [endothelium-dependent flow-mediated dilation (FMD)], microvascular reactivity [reactive hyperemia index (RHI, Endo-PAT2000)] and arterial stiffness [pulse wave velocity (PWV), Sphygmocor Inc.] were measured at rest and 30-min after MS.

Results: Of 457 patients with CAD aged 63±9 years (75% male), 87 (15.5%) developed MSIMI. FMD decreased [median (IQR) change: -0.8 (-2.5 – 0.6)%, p=0.002], PWV increased [median (IQR) change: 0.3 (-0.7 – 1.2) m/s, p=0.025], but there was no change in RHI after MS (Figure). There were no significant differences in either the baseline or post-MS vascular measures between patients with and without MSIMI (Figure). Conclusion: MS is associated with impairment of conductance vessel but not microvascular
endothelial dysfunction and with increased arterial stiffness. The magnitude of these alterations is not a predictor of MSIMI in CAD.

**#63 (afternoon session)**

**Poldip2 downregulation mediates proteasome inhibition during hypoxic conditions**
*Paredes F, San Martin A*

The Polymerase delta interacting protein 2 (Poldip2) is part of the mitochondrial nucleoid; however, the role of Poldip2 in mitochondrial function and cellular metabolism is unknown. In vascular smooth muscle cells, Poldip2 expression is downregulated by hypoxia. Additionally, when we downregulate Poldip2 expression using siRNA, Poldip2 deficient cells repress mitochondrial respiration and increase glycolytic metabolism. The Ubiquitin proteasome system (UPS) is the primary system that mediates the degradation of short-lived regulatory proteins and the removal of damaged soluble proteins. Importantly, UPS activity is inhibited in metabolic diseases by 26S acetyl-glucosaminacylation. We reasoned that Poldip2 downregulation is responsible for proteasome activity inhibition during hypoxic conditions and that this inhibition is the consequence of increased glycolytic metabolism. Indeed, our data indicate that Poldip2 deficient cells display impaired protein degradation by the UPS as evident by accumulation of Ubiquitin-linked proteins. Additionally, O-GlcNAcylation of proteins is significantly increased in Poldip2 deficient cells. More importantly, Poldip2 downregulation inhibits the UPS activity in normoxia and its overexpression under hypoxia is capable to restore hypoxia-induced UPS inhibition. Based on these observations, we propose that during hypoxia, Poldip2 downregulation-mediated metabolic reprogramming induces the inhibition of the UPS by an OGlcnAcylation dependent mechanism. This mechanism connects proteasome activity to mitochondrial function and may allow cells to respond to metabolic needs.

**#51 (morning session)**

**Increased prevalence of colorectal carcinoma in a human immunodeficiency + cohort: a single center retrospective study**
*Patel K, Sabharwal N, Spense L, Nguyen MLT, Marconi VC, Mehta C, Chawla S*

Introduction: Improved life expectancy following the advent of anti-retroviral therapy (ART), has resulted in an increase in Non-AIDS Defining Cancers (NADCs) in patients with HIV. Published data remain inconsistent on the prevalence of colorectal carcinoma (CRC) and outcomes of colon cancer screening in this cohort. Our aim was to evaluate the prevalence of colorectal neoplasms in HIV + patients undergoing screening colonoscopy and determine predictors of adenomas and CRC within this group.

Methods: We performed a single-center retrospective cohort study of HIV + patients undergoing screening colonoscopy between 2012-2015. Known and hypothesized predictors of CRC and polyp characteristics were assessed through bivariate analyses.

Results: Our cohort of 168 patients had a mean age of 56.7 yrs (SD 5.2), was predominantly African American (86%) with 62% (104) men. 93% of patients were on ART and 45% had an undetectable HIV RNA. The prevalence of all adenomas was 27.4 % (46/168) and for advanced adenomas it was 6.6% (11/167). CRC was detected in 3% of patients (5/167). Bivariate analysis of demographic and risk factors showed that CD4 count, history of ART, Hepatitis B or C status were not associated with adenoma amongst the HIV cohort.

Discussion: Our cohort interestingly showed a notably higher rate of CRC (3%) compared to large, population-based screening colonoscopy studies (0.1-0.5%) and also other prior HIV cohorts, suggesting an increased risk in the HIV population during the ART era. This study reinforces the need for further research and refinement of colon cancer screening recommendations for individuals with HIV.

**#5 (afternoon session)**

**Prospective comparison of magnetic resonance imaging conditional and non-conditional cardiac implantable electronic devices**
*Patel AU, Shah AD, Lloyd MS*

Objectives: This study compared the safety of non magnetic resonance imaging (MRI) conditional and MRI conditional pacing and defibrillator systems with particular attention to clinically actionable outcomes.

Background: While recipients of new MRI conditional pacemaker and defibrillator systems may undergo MRI scanning safely, safety and regulatory concerns persist regarding such scanning in recipients of non-MRI conditional systems.

Methods: Patients with any cardiac device who were referred for MRI were prospectively enrolled at a single center and underwent scanning at 1.5 Tesla. Pre and post scan lead characteristic changes, system integrity and symptoms and were compared between non- MRI conditional and MRI conditional devices.

Results: 105 patients were evaluated allowing for comparison of 96 scans with non MRI conditional devices and 17 scans with MRI conditional devices. The cohort included those with pacemaker dependency, defibrillator and cardiac resynchronization devices. Small changes were observed in lead characteristics following scanning, however there was no significant difference when comparing non-MRI and MRI conditional devices. Lead parameter changes did not require lead revision or...
Conclusions: Performance of MRI scanning in patients with cardiac devices can be performed safely at 1.5 T. Utilization of MRI conditional devices did not afford additional protection secondary to the excellent safety profile associated with non- MRI conditional devices.

#22 (afternoon session)

Docosahexaenoic acid reverses palmitate induced impairment of protein synthesis rate and eIF2α phosphorylation in cultured skeletal muscle

Perry BD, Rahnert J, Xie Y, Zhang P, Espinosa D, Price SR

Circulating levels of saturated fatty acids, such as palmitate (PA), are elevated in type II diabetes mellitus. In skeletal muscle, PA impairs insulin sensitivity, induces ER stress and impairs protein synthesis. Both insulin resistance and ER stress are reversed with treatment of n-3 polyunsaturated fatty acids like docosahexaenoic acid (DHA). However, it remains unclear whether DHA reverses the PA-induced impairment in protein synthesis and which signaling pathways are involved. This study investigated the effects of PA and DHA on protein synthesis and related proteins, including eukaryotic initiation factor 2α (eIF2α) and p70S6k in skeletal muscle. We also investigated 5'AMP-activated protein kinase (AMPK), due to its potential role in reducing ER stress and altering protein synthesis through mTOR signaling. C2C12 myotubes were treated with vehicle (2% BSA), DHA (100 μM), PA (500 μM) or co-treated with PA+DHA. Protein synthesis was inhibited after 6h (-34.7%) and 24h (-40.8%) PA treatment and restored by DHA co-treatment. Phosphorylation of eIF2α, which reduces eIF2B activity and subsequently protein translation, increased with 6h (2-fold) and 24h (3.4-fold) PA treatment and was reversed by DHA. Conversely, p-p70S6k was increased with 6h PA treatment, but unaffected by DHA. AMPK phosphorylation increased with 6h PA treatment (24.9%), but was reduced at 24h (-31.2%). Therefore, PA induced a global reduction in protein synthesis consistent with increased p-eIF2α, but not p-p70S6k in cultured skeletal muscle. Despite the reported beneficial effects of AMPK in limiting PA-induced ER stress, impaired protein synthesis and increased p-eIF2α did not coincide with reduced p-AMPK.

#34 (afternoon session)

Plasmodium knowlesi zoonotic malaria: clinical and research insights from Malaysia

Peterson MS, Singh B, Joice RC, Jones D, MaHPIC Consortium, Galinski MR

Worldwide malaria causes up to 500,000 deaths yearly, and remains a significant barrier to economic development in endemic regions, despite progress in its control. Canonically, malaria in humans is caused by four Plasmodium species, P. falciparum (the most virulent), P. vivax, P. ovale, and P. malariae. Recently, Plasmodium knowlesi, a parasite known to cause malaria in monkeys and thought to be a cause of rare spillover events in humans, has been recognized as the most common cause of human malaria in Malaysian Borneo. This zoonosis has emerged as the fifth human malaria parasite. Spillover of knowlesi malaria threatens malaria control efforts in the region, as the zoonotic nature of the parasite challenges conventional malaria prevention strategies. Presentation and clinical outcome of knowlesi malaria are variable, and range from uncomplicated to fulminant disease including kidney failure and death. Further complicating this spectrum of disease are barriers to obtaining medical care, as well as host and vector ecology. To better understand the biological determinants of host tolerance and susceptibility responsible for variable presentation and outcome, a systems biology approach will be implemented to compare host metabolomic profiles from serum samples taken from individuals confirmed to be ill with knowlesi malaria and healthy controls. Here we present a firsthand account of knowlesi malaria presentation and treatment in Kapit, Malaysia, and a discussion of Plasmodium knowlesi ecology, pathophysiology, and research questions to be explored.

#6 (morning session)

Living in a food desert fails to predict heart failure outcomes

Phoakan S, DeMoss B, Hammadah M, Kelli HM, Gupta D

Objective: This study sought to determine whether living in a food desert or an area with low access to fresh food impacts 30-day readmissions and total hospitalizations for heart failure patients.

Methods: We identified patients admitted to a university hospital between 01/01/2013 and 12/31/2013 with a primary diagnosis of heart failure. We entered patients’ zip codes into the USDA Food Access Research Atlas to identify those who live in areas with low access to fresh food (> 1 mile in urban areas or > 10 miles in rural areas from a supermarket) or food deserts (additional stipulation of median income is ≤ 80% of statewide median). We used regression analysis to compare 30-day readmissions and total hospitalizations for patients living in low-access or food deserts vs. living in adequate-access areas.

Results: There was 2063 hospitalizations from 1598 unique patients in this sample (54% male, 41.1% African American, mean age 65±17 years, mean EF 41±19%). 789 (49.4%) patients lived in low-access areas and 318 (19.9%) lived in food deserts. 211 (13.2%) patients had at least one 30-day readmission. We used regression analysis to compare 30-day readmissions and total hospitalizations for patients living in low-access or food deserts vs. living in adequate-access areas.
Continuous cardiac monitoring in hospital settings
Pinzon I, Seedahmed M

Overuse of continuous cardiac monitoring (CCM) for patients who do not meet American Heart Association guidelines can be costly and lead to unnecessary medical care. The goals of CCM in hospital settings include heart rate and basic rhythm determination, diagnosis of complex arrhythmias, myocardial ischemia, and prolonged QT interval. The American Heart Association rating system divides patients by class to determine the need for CCM. This retrospective study showed the utilization of CCM in a community hospital. A total of 1659 patients were evaluated: Female 54.7% (n=908) and Male 45.3% (n=751), age: 70.3 ±15.1, hospital length of stay 4.1±3.8 days. Total patients with CCM during hospitalization: 63.5% (n=1048). Patients with diagnosis of cardiac arrhythmias (n=623), 83.6% with CCM, diagnosis of myocardial infarction (n=34), 82.3% with CCM, and cardiac arrest (n=27) 74% with CCM. Mortality (n=82) 18.3% without CCM and no indication, 8.5% without CCM and with clear indication, 28% with CCM but with no indication, and 45% with CCM and indication. Interestingly, 31.5% (n=330), of the hospitalized patients who received CCM did not meet criteria for CCM use. In summary, with this study we see the urgent need to develop a standard protocol for CCM in our hospital, which will result in better patient care during hospitalization and avoid unnecessary use of CCM among patients who do not meet the guidelines.

Incidence and survival in gastric adenocarcinoma and early gastric adenocarcinoma in the United States
Pokala SK, Chen Z, Keilin S, Cai Q, Willingham FF

Introduction: The incidence and survival in gastric adenocarcinoma in the United States may differ considerably from that reported in Eastern countries, however little published data on this topic exists. This study provides updated measures of the incidence and survival in gastric adenocarcinoma and early gastric adenocarcinoma in the US.

Methods: Incidence and survival data for all gastric tumors were abstracted from the national SEER database, between 2004-2013. Early stage was defined as Tis, T1a, T1b, and T1NOS. The Kaplan-Meier method was used to calculate relative survival. Survivals were compared using the log-rank (Mantel-Cox) test.

Results: 63,723 cases of gastric tumors were initially abstracted from the database. After exclusions, 6,886 cases of gastric tumors were analyzed for incidence. The incidence of all gastric tumors between 2004-2013 was 1.04 per 100,000 person-years. 74.2% were adenocarcinomas and 14.1% were signet ring cell carcinomas. The incidence between 2004-2013 of gastric adenocarcinomas was 1.04 per 100,000 person-years for all stages and .48 per 100,000 person-years for early stage disease. Both all and early stage disease incidences varied from year to year, without a clear trend over time. 5,561 cases of gastric adenocarcinoma were analyzed for survival. The 5-year survival of early stage gastric adenocarcinoma was 87.30%.

Conclusion: Gastric adenocarcinoma represents the majority of gastric tumors occurring in the US. From 2004 to 2013, incidence varies from year to year without a trend over the studied period. While gastric cancer is considered an aggressive tumor, the 5-year survival for early stage disease is greater than 85%.
**Asymptomatic hypoglycemia in hospitalized patients with type 2 diabetes**


The impact of asymptomatic hypoglycemia in the hospital is not known. This prospective study determined the frequency, risk factors and clinical outcomes of symptomatic and asymptomatic hypoglycemia (<70 mg/dl) in patients with type 2 diabetes. Point-of-care glucose testing was performed before meals and at bedtime. Hypoglycemia was identified by electronic medical record and assessed with a pre-set questionnaire. The study included 134 subjects with mean age 55.4±12.6 yrs, 47% female, admitted to 2 Emory hospitals between 4/2015 and 12/2015. Patients were treated with basal insulin (27%), basal bolus (38%), sliding scale (14%), oral agents ± insulin (10%), or no antidiabetic regimen (10%). A total of 69 patients (51.4%) were asymptomatic and 65 (48.5%) had ≥1 symptom of hypoglycemia. Signs and symptoms of hypoglycemia were more common in women (58.7% vs. 39.4%, p=0.03) and in patients with higher HbA1c (3.2±2.9% vs 7.7±2.3%, p<0.001). Adrenergic symptoms including sweating (66%), anxiety (48%), tremors (51%) and palpitations (22%) were more common than neuroglycopenic findings such as confusion (49%), blurred vision (35%) and slurred speech (22%). Duration of diabetes, BMI, medicine vs. surgery service, beta-blockers, length of hospital stay or mortality did not differ between groups. Risk factors for hypoglycemia were poor oral intake/nausea (43%), eGFR <60 ml/min (52%) and heart failure (10%). In summary, more than half of hypoglycemic episodes were asymptomatic in hospitalized patients with diabetes. Women and patients with poor glycemic control were more likely to experience symptoms. Frequent glucose monitoring is needed to prevent potential complications associated with hypoglycemia.

**Inhibition of PDE7 reduces inflammatory response following renal ischemia/reperfusion injury**

Reis WR, Blount MA

Ischemia/reperfusion (I/R) injury is an unavoidable consequence after kidney transplantation and is clinically associated with kidney graft rejection and/or dysfunction leading to progressive interstitial renal fibrosis and declining renal function. Because elevated cAMP can offset immune response, identification of a protein to increase kidney cAMP levels may provide a viable option to prevent I/R injury. This study aimed to understand the benefits of raising renal cAMP levels through PDE7 inhibition for treating the immune response following I/R insult. Preliminary qRT-PCR studies showed that PDE7 inhibition reduced expression of harmful cytokines (IL-2, IL-6, IL-12, IL-18) and chemokines (CCL2, CCL5) to sham levels, when stimulated with TNFα in HK-2 cells. To model this in vivo, we surgically inhibited bilateral renal circulation of Sprague-Dawley rats for 30 minutes following a 24-hr injection of the PDE7 inhibitor TC3.6. Blood, urine and kidney tissue were harvested at the time of sacrifice 24-hr after surgery. qRT-PCR analysis of kidney tissue showed that I/R injury increased expression of pro-inflammatory cytokines and chemokines in sham treated rats; however, in rats treated with TC3.6, cytokine and chemokine expression was reduced to sham surgery levels. This was noted with the cytokine IL6 and the chemokine CCL5. Blood Urea Nitrogen (BUN) levels showed a similar pattern in the samples. Reduced cytokine and chemokine expression, as well as reduced BUN levels in treated versus untreated I/R rats, is evidence that PDE7 inhibition may be an effective pretreatment prior to kidney transplant to prevent the necessary I/R injury associated with the surgical procedure.

**ZBTB46 regulates cell proliferation and cell cycle in endothelial cells and may have an atheroprotective role**

Rezvan A, Sun HY, Wang, Y, Kumar S, Jo H

Background: ZBTB46 is a transcription factor expressed in endothelial cells (EC) and its role in EC gene regulation is unknown. EC activation in areas exposed to disturbed flow is the initial step in atherosclerosis. We hypothesized that ZBTB46 expression is reduced in areas exposed to disturbed flow, leading to changes in gene expression and increased atherosclerosis.

Methods: We used the cone and plate model, to examine ZBTB46 expression in response to disturbed flow in vitro and the mouse partial ligation model and ZBTB46 KO mice for in vivo studies. siRNA and overexpression via viral vectors were used to assess the role of ZBTB46 on EC gene expression and cell proliferation. EC gene expression was assessed using gene arrays and qPCR. Cell cycle was assessed using flowcytometry.

Results: ZBTB46 is expressed in both human and murine ECs, and is down-regulated by disturbed flow both in vivo (by %45, p<0.05) and in vitro (by %75, p<0.05). ZBTB46 KO led to significant gene expression changes in ECs in vivo (>150 differentially expressed genes) and increased atherosclerosis in areas not exposed to disturbed flow (4.25 fold, p<0.05). Pathway analysis suggested an anti-proliferative and anti-inflammatory role for ZBTB46 in ECs. ZBTB46 overexpression in ECs led to increased number of cells in the G0/G1 phase (%79 vs 56%, p<0.05).

Conclusion: ZBTB46 is regulated by shear stress in ECs, and appears to be atheroprotective by keeping ECs in a quiescent state. Targeted manipulation of ZBTB46 expression may have therapeutic potential in conditions such as atherosclerosis.
Racial disparity in the JNC-8 and SPRINT SBP targets impact on cognitive function: analysis of the health ABC

Rosenberger K, Hajjar I, Goldstein F, Kulshreshtha A

Background: Guidelines have provided multiple targets for systolic blood pressure (SBP) in older adults but their impact on cognition is unknown. The SPRINT trial has suggested a target SBP<120. Concerns have been raised regarding a low target on cognition. Most guidelines provide similar targets for African Americans and Caucasians. Objective: To assess the association between SBP targets and cognition and the racial differences in this association.

Materials and methods: Health ABC consisted of a sample of 3075 healthy adults older than 70. Cognition was assessed using three cognitive tests (3MS, CLOX1, and DSST). Systolic blood pressure was separated into four different classes based on the mean of two seated readings at each visit. Our analysis used mixed models with repeated measures.

Results: Our sample included 1904 with hypertension (1495 were treated, age = 73.7, 55.2% women, 54.3% white). SBP cutoff was associated with 3MS decline (p-value 0.02). The greatest decline was in those with SBP>=150 mmHg (yearly decline=-2.2, p<0.0001), those with SBP<120 mmHg (yearly decline=-1.0, P<0.001) and those <150 and <140 (-0.7 and -0.8 respectively, both P<0.0001). The rate of decline in 3MS was steeper in the African American population but this racial disparity decreased as the target SBP was lower (p-value race*visit*SBP group=0.009). There was no association with DSST or CLOX1.

Conclusion: Target SBP of <150, <140 or <120 were associated with similar cognitive trajectory. Lower targets have greater impact on African Americans and may decrease cognitive disparity. A target similar to SPRINT was not associated with worse cognitive outcome.

#3 (morning session)

Does experience matter? Implications for community consultation for research in emergency settings

Scicluna VM, Ali MK, Pentz RD, Wright DW, and Dickert NW

Introduction: Community consultation (CC) is required for research using an exception from informed consent (EFIC) in the US. Uncertainty persists regarding best practices for CC; specifically whether to prioritize geographically-defined communities or individuals with experience with the condition under study. Understanding the impact of personal disease experience on views of EFIC research is important for designing CC efforts and interpreting their results.

Methods: This study was a secondary analysis of surveys administered to 2612 CC participants at 12 sites for ProTECT III: the Progesterone for Traumatic Brain Injury trial, a phase III, randomized, placebo-controlled trial using EFIC. Key survey domains included personal experience with traumatic brain injury (TBI) and acceptance of both hypothetical personal enrollment under EFIC and EFIC use in general in ProTECT. Descriptive statistics and multivariable regression models were used to explore relationships between key domains.

Results: 49% of CC participants were either TBI patients, had a family member/loved one with TBI or knew someone else with TBI. Participants with personal TBI experience were slightly more accepting of hypothetical personal EFIC enrollment (Adjusted OR 1.14-1.54) and EFIC use in general (AOR 1.06-1.39) than those without it. In a sub-group analysis based on race, a trend in the opposite direction was observed among black participants. Conclusions: Personal TBI experience was associated with increased acceptance of EFIC, except among black participants. Heterogeneity of the effect of personal disease experience further supports the inclusion of individuals with disease experience in CC efforts and highlights the importance of engaging minority participants.

#13 (afternoon session)

Patient centered approaches to research enrollment (P-CARE)


Introduction: Informed consent for clinical trials in acute myocardial infarction (MI) and stroke is complicated by time pressure, severe illness, and stress. Insufficient data exist regarding patients’ and surrogates’ experiences; these data may help to maximize respect for patients while facilitating important trials.

Methods: We interviewed patients or surrogates who consented to enroll in ST-elevation MI (n=47) or acute stroke trials (n=58) at 3 sites from 2011-2016. Structured interviews focused on trial recall, perceptions of the consent process, and preferences regarding involvement. Questions were closed-ended with open-ended probes. Descriptive and bivariate statistics were used to characterize responses and explore relationships between key domains and demographics.

Results: Of 105 participants, 6 stroke and 15 MI participants did not recall being in a trial. Among the remaining 84, 98% felt they were treated with dignity. More MI trial participants recalled the consent conversation lasting less than 5 minutes (50% MI vs. 22% stroke, p<0.001). MI participants were also less likely to report reading the consent form (34% MI vs. 71% stroke, p<0.001) and less likely to recall asking questions before enrolling (19% MI vs. 62% stroke,
p <0.001). 90% of participants were glad they were asked for permission before study inclusion. 40% did not recall anyone talking with them about the study after enrollment.

Conclusions: Participants in acute MI and stroke trials generally reported positive experiences with consent. Despite intrinsic challenges, most participants appreciate being asked for permission before enrollment. Opportunities exist to improve communication pre- and post-enrollment.

#16 (morning session)

Cognitive impairment in Parkinson disease did not predict benefit from behavioral intervention for urinary symptoms
Landry AN, Sesay M, Goldstein FC, Johnson 2nd TM, Burgio KL, Goode PS, Juncos JL, Vaughan CP

Objective: Urinary incontinence (UI) is a common non-motor symptom in Parkinson disease (PD). This study sought to determine if baseline cognitive function predicts benefit from behavioral intervention to reduce UI in PD.

Methods: Participants who completed treatment in an ongoing randomized controlled trial of behavioral intervention for urinary symptoms in PD were grouped based on their response to a validated Benefit assessment (Benefit: better/much better; No Benefit: no change, worse, much worse). The Benefit assessment was conducted 8 weeks after randomization to either continuous bladder diary alone (self-monitoring) or pelvic floor muscle exercise-based behavioral therapy. A screening test of overall cognitive function and domain-specific neuropsychological assessments were conducted at baseline. A Montreal Cognitive Assessment (MoCA) score <18/30 was an exclusion criterion. UI episodes were recorded in 7-day bladder diaries completed at baseline and 8 weeks and change was calculated as a percent.

Results: The No Benefit group (n=8) did not differ from the Benefit group (n=20) with respect to gender, age, baseline overall cognitive function (MoCA), years with PD, or PD motor symptom severity. The Benefit group reported greater percent reduction in weekly UI episodes over 8 weeks (72.0 ± 44.6 percent) compared to the No Benefit group (41.8 ± 41.8 percent, p = 0.025). None of the tests of cognitive function (MoCA or domain-specific) predicted persons reporting Benefit from a behavioral intervention for UI.

Conclusion: Behavioral intervention for UI provided a favorable treatment option for persons with PD, even in the setting of mild cognitive dysfunction.

#7 (morning session)

Cerebral blood flow is associated with executive function in hypertensive African Americans but not Caucasians
Sharma H, Dejian Q, Hajjar I

Introduction: Hypertension is associated with declines in executive function and cerebral perfusion. Hypertension is also associated with worse outcomes in African Americans. The purpose of this study was to evaluate the impact of cerebral blood flow on executive function in Caucasians and African Americans (AA) with hypertension.

Methods: Individuals with known hypertension (mean age=67.68 yrs) were enrolled in the CALIBREX clinical trial and underwent an MRI scan and cognitive function assessment that included the trail making test (TMTB). The MRI scan included the non-invasive method to assess cerebral perfusion, arterial spin labeling (ASL) and T1-weighted anatomical sequences. This analysis was conducted on 35 participants. Cerebral blood flow (CBF) maps were computed using ASL toolbox and Statistical parametric mapping software. Regression analysis was conducted to assess the relationship between the CBF values and the TMTB scores in AA and Caucasians.

Results: Hypertensive AA showed a statistically significant relationship between the CBF and TMTB scores [F(4,16)=4.96, p=0.009] with an R2 of 0.554. Whereas, there was no relationship between CBF and TMTB scores in Caucasians [F(4,8)=0.127, p=0.96, R2=0.6].

Conclusion: This study suggests that the impact of cerebral perfusion is greater on executive function only in hypertensive AA. These findings support the hypothesis that cognitive decline in AA is more likely to be related to vascular factors.

#10 (morning session)

Mesenchymal stem cells require CD73 activity to reduce leukocyte associated inflammation following myocardial ischemia-reperfusion injury

Introduction: Cell death following myocardial ischemia-reperfusion (MI/R) injury releases toxic metabolites in the interstitium, eliciting a potent immune response. Therapeutic use of mesenchymal stem cells (MSCs) represents a potential strategy to target this cascade and reduce myocardial necrosis. This study examines whether implantation of MSCs regulates excess inflammation following MI/R and specifically investigating whether CD73 mediated conversion of ATP/ADP to anti-inflammatory adenosine is a potential mechanism for MSCs immunomodulatory capacity in vivo.

Methods: Rats underwent 30 minutes of MI/R injury and were treated with saline, encapsulated MSCs (eMSCs), or
Corticobasal Degeneration: a case study

psychosocial function in an individual with Adapted tango effects on motor, cognitive and subsequent cardio-protection will be pursued.

microenvironment. Future studies to identify whether CD73 is critical for cultivating an anti-inflammatory microenvironment. eMSCs pretreated with CD73 inhibitor (APCP-eMSC). Inflammation was measured from myocardium 1 day following injury. Quantification of H$_2$O$_2$ was performed by amplex red assay and enumeration of leukocyte infiltration by flow cytometry. Longitudinal cardiac function was measured by echocardiography.

Results: Infiltrating CD45+ leukocytes were reduced in animals treated with eMSCs compared to saline. This effect was reversed by inhibition of CD73 with APCP. Cell subsets including MPO+ neutrophils and CD68+ macrophages were also reduced by eMSC therapy (N=4, P<0.05). H$_2$O$_2$ production was attenuated by eMSCs therapy (N=6, P<0.05). eMSCs improved cardiac function compared to saline as early as 7 days following injury and persistent benefit for up to 28 days by global longitudinal strain (N=6, P<0.05).

Conclusion: This is the first study to demonstrate MSCs reduce ROS production in vivo and MSC-CD73 activity is critical for cultivating an anti-inflammatory microenvironment. Future studies to identify whether CD73 activity is necessary for inhibition of immune cell activity and subsequent cardio-protection will be pursued.

Adapted tango effects on motor, cognitive and psychosocial function in an individual with Corticobasal Degeneration: a case study

Corticobasal degeneration (CBD), involving atrophy of the cerebral cortex and basal ganglia, shares symptoms (e.g., tremor, rigidity, bradykinesia, and postural instability) with Parkinson’s Disease (PD). With both PD and CBD, quality of life (QOL) declines over time. Effective treatments are limited for the more rapidly progressing CBD. Adapted Argentine Tango (AT) is a successful mobility treatment for PD, and may address CBD symptoms. An individual with CBD (alias: YD; male, 63 years-old, CBD duration= 2 years) was evaluated with motor, cognitive and psychosocial measures before, immediately after, and 1 month after 20, twice weekly 1.5 h-long AT lessons over 12 weeks. Immediately after AT, YD improved on disease-related motor symptoms (pre = 63, post = 51), and reported fewer non-motor symptoms (pre=9, post=6). YD improved on mobility (Four Square Step Test: pre=20.9s, post=17.9s and Timed Up and Go: pre=12.1, post=11.5,) but declined on tests of endurance, and dynamic balance. YD improved on cognitive flexibility (Trails B-A pre =85.4s, post=43.5) and planning (Tower of London Achievement score: pre=12, post =19), but declined on a body position spatial cognition task (pre=16, post=9). YD reported improved balance confidence (pre=51.9, post=61.3) but increased depression after treatment (BDI pre = 9, post=15). PD-related QOL did not change. The gains were variably maintained. YD reported enjoying the classes. His spouse and the instructors anecdotally reported enhanced mobility. AT may have slowed disease progression, improved mobility and aspects of cognition in this individual, but the gains were variable and variably maintained. Further group study in CBD is warranted.

B cell Phenotype in ANA+ and SLE pediatric patients

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects both adults and children. The pediatric onset of SLE has comparable diagnosis criteria and presents with similar symptoms, however the exact cause of the disease is unknown in adults and children. Production of auto-antibodies by B cells contributes significantly to autoimmune pathogenesis and can also provide diagnostic markers for disease. Several SLE therapies target B cells, and studies are currently ongoing to better understand the phenotypic signature of B cells in adults with SLE. Much less is known about B cells in pediatric SLE patients. In some children serological tests indicate the presence of abnormal autoantibody levels (ANA+), which is one of the diagnostic criteria for SLE, but they do not exhibit any clinical symptoms of autoimmunity or their symptoms do not meet the threshold required for a full diagnosis. Some of these children are later diagnosed with SLE, so we are studying the B cell phenotype of ANA+ children and SLE children to determine if there are similarities in phenotypic patterns. We are also comparing the B cell phenotypic patterns with those of adult SLE patients, healthy adults, and healthy children. Additionally, we are following patients longitudinally to see if the phenotypic patterns change over time or in association with changes in clinical symptoms or diagnosis.

Effects of doxorubicin on cellular bioenergetics and metabolism in platelets

It has been observed that cancer progression has been associated with platelet activation, and as a result, platelets have become an ideal model to study the effects of chemotherapeutic agents on cellular bioenergetics and changes to cell metabolism. Doxorubicin (Adriamycin) is a chemotherapeutic agent used in the treatment of many cancer types. Doxorubicin functions through the intercalation of DNA in order to arrest the cell cycle; however, adverse effects such as cardiotoxicity. Interestingly, Doxorubicin has also been found to be a one-electron acceptor forming a semiquinone radical leading to the formation of superoxide. We hypothesize that the increased superoxide alters both the cellular bioenergetics and the metabolism of platelets leading to altered cellular function. Using acute sub-lethal concentrations of doxorubicin, we treated platelets isolated from healthy volunteers and monitored changes to cellular bioenergetics.
using extracellular flux analysis. It was found that as the concentration of doxorubicin increased, both basal and non-mitochondrial oxygen consumption rates (OCR). Stored platelets procured from the blood bank were also tested, and doxorubicin also increased both basal and non-mitochondrial OCR. Thrombin activation was also decreased as concentrations of doxorubicin increased, implying that doxorubicin also interferes with thrombin activation. Platelet aggregation was also decreased by doxorubicin. These results indicate that the redox cycling of doxorubicin alters platelet function through changes in cellular bioenergetics and metabolism, and provides novel information about the mechanisms of doxorubicin.

#15 (afternoon session)

Implantation of PA-RGDS nanomatrix encapsulated human lymphatic endothelial progenitor cells to ameliorate lymphatic function in arm lymphedema model

Sohn YD, Andukuri A, Lee SJ, Cho SG, Yoon YS

Introduction: Despite substantial advances, therapeutic options for management of lymphedema are limited. Recently, we identified human peripheral blood (PB)-derived lymphatic endothelial progenitor cell (LEPC) as an optimal candidate for lymphatic neovascularization and tested the therapeutic effects of the biomaterial (PA-RGDS) based delivery on arm lymphedema model.

Methods: Forearm lymphedema was induced via lymphatic vessel and lymph node dissection of the athymic nude mice. Then PDPN+ LEPCs (2.5 x 10^5) were implanted into the edematous arm with or without encapsulation in PA-RGDS. The changes in arm circumference of the lymphedema-induced mice were measured over the edema development. NIR fluorescence dye was injected into edematous arm and monitored lymphatic function 24 hours after the injection by near infrared imaging.

Results: During the development of lymphedema, mean circumference of the arms of lymphedema-induced mice treated with PA-RGDS encapsulated LEPC (LEPC+PA-RGDS) group was significantly lower than other controls groups. LEPC+ PA-RGDS implanted group had significantly reduced residual NIR dye intensity in the arm lymphedema model compared to other controls. Finally mice were evaluated through histochemical examination from which we identified remodeling of skin thickness, incorporation of host lymphatic vessels, and effects on lymph capillary density were significantly improved in the PA-RGDS encapsulated LEPC groups.

Conclusion: PA-RGDS encapsulated LEPC transplantation accelerates healing of lymphedema in murine lymphedema models, and transplanted LEPCs contribute to the formation of new lymphatic vessels in the edematous tissue through lymphatic neovascularization. Therefore, PA-RGDS encapsulated LEPCs may represent a novel therapeutic option for the treatment of lymphedema.

#46 (afternoon session)

Urea transport in the collecting duct, regulated by an endothelin/nitric oxide signaling pathway, is required for sodium reabsorption

Sun MA, Rogers RT, Blount MA

Through several regulatory mechanisms, the kidney modifies blood pressure by controlling fluid homeostasis. Nitric oxide (NO) production in the collecting duct regulates sodium and water reabsorption to stabilize blood volume by regulating transporter function. Ablation of the collecting duct urea transporters, UT-A1 and UT-A3, induces polyuria in UT-A1/A3 null (KO) mice. The inability of these mice to reabsorb water leads us to speculate that NO production is altered. Corroborating previous reports, urinary nitrate/nitrite levels were increased 3-fold in UT-A1/A3 KO mice. Investigation of nitric oxide synthase (NOS) mRNA expression levels revealed that NOS2 and NOS3 expression were unchanged in UT-A1/A3 KO medulla compared to WT; however, NOS1 expression was increased 40-fold in inner medulla of UT-A1/A3 KO mice. Because collecting duct endothelin (ET-1)/NO signaling pathway modulates pressure-natriuresis, we investigated this pathway in the inner medullary collecting ducts of UT-A1/A3 KO mice. We found that serum aldosterone levels and mineralocorticoid receptor protein expression, regulators of ET-1 concentration, were increased and endothelin type-B (ETB) receptor protein expression, the target of ET-1, was also increased in UT-A1/A3 KO mice compared to WT. Urinary sodium excretion in UT-A1/A3 KO was increased 57% and blood pressure was slightly lower in these mice compared to WT in accordance with the natriuretic and antihypertensive effects of ET-1 and ETB expression. Renal handling of sodium and water has always been linked processes in regulation of blood volume. The present studies suggest that urea handling in the collecting duct, acting through endothelin-simulation of NOS1, also regulates sodium reabsorption.

#7 (afternoon session)

Specific detection of bacterial infection associated with cardiac implantable electronic devices


Background: Bacterial infection is a serious complication of implantable electronic devices, and the early detection has been a clinical challenge. Our first generation PET tracer, F18-F-maltohexaose in which F18 was conjugated with maltohexaose with a linker, accumulated in the infected area; however, the signal/noise ratio decreased rather rapidly. Therefore, we developed a second generation PET tracer, methyl O-(alpha-D-glucopyranosyl)-(1-4)-S-(alpha-D-glucopyranosyl)-(1-4)-6-deoxy-6-fluoro-4-thio-alpha-D-glucopyranoside (F-18-6-FTMT) in which maltose and F18 containing glucose analogue are connected with sulfa molecule, and we evaluated whether
this second generation tracer is useful for the detection of bacterial infection in the early stage.

Methods and results: To evaluate whether F-18-6-FTMT would accumulate in the infected area, Sprague-Dawley rats were implanted with stainless steel device mock-ups and were injected with 1 X 10^9 CFU/ 0.1 ml Staphylococcus aureus around the mock-ups on post-operative day 4. On post-operative day 6, the infected rats and the control rats were injected with 200 uCi of F-18-6-FTMT and scanned with micro-PET/CT for 90 min. The accumulation in the infected area was seen in the infected rats even 90 min after the injection of tracer. The signal/noise ratio around the mock-up area was 1.93 A± 0.17 and was stable for 90 min in the infected rats.

Conclusion: F-18-6-FTMT PET imaging detected bacterial infection with high sensitivity in a rat model of infections associated with medical devices, suggesting the potential utility of this imaging agent in detecting bacterial infections in man.

#14 (afternoon session)

IGF-1 degradation by mouse mast cell protease 4 promotes delayed cell death in post-ischemic hearts

Tan L, Tejada T, Torres RA, Calvert J, Lefer DJ, Naqvi N, Husain A

Heart disease is a leading cause of death in adults. Here we show that a few days after coronary artery ligation and reperfusion, the ischemia-injured heart elaborates the cardioprotective polypeptide, insulin-like growth factor-1 (IGF-1), which activates IGF-1 receptor prosurvival signaling and improves cardiac left ventricular systolic function. However, this is antagonized by the chymase, mouse mast cell protease-4 (MMCP-4), which degrades IGF-1. We found that MMCP-4 deficiency, resulted in sustained IGF-1 levels and IGF-1 receptor prosurvival signaling post-I/R. MMCP-4 deficiency markedly reduced late, but not early, infarct size (~50% reduction: n=5--7, p value= 0.001) by suppressing IGF-1 degradation and, consequently, improving cardiac function (EF: 26% greater, n=21, p value= 0.001) and adverse structural remodeling. Our findings represent the first demonstration of tissue IGF-1 regulation through proteolytic degradation and suggest that chymase inhibition may be a viable therapeutic approach to enhance late cardioprotection in post-ischemic heart disease.

#38 (morning session)

Contribution of T cells to RANKL/OPG imbalance and bone loss in HIV infection

Titanji K, Vunnava A, Foster A, Sheth AN, Lahiri CD, Ofotokun I, Weitzmann MN

HIV infection is associated with high rates of osteoporosis and bone fracture. Bone resorbing osteoclasts are regulated primarily by the ratio of the key osteoclastogenic cytokine, Receptor activator of nuclear factor-κB ligand (RANKL), to that of its physiological inhibitor, Osteoprotegerin (OPG). B cells are a key source of OPG and RANKL and we previously reported that HIV infection leads to a decline in B cell OPG and an increase in RANKL. However, the contribution of T cells to RANKL/OPG imbalance in HIV infection has not been studied. In this study intracellular T cell RANKL and OPG production was quantified by flow cytometry in 58 HIV-uninfected (48.3% Male and 82.5% Black) and 62 antiretroviral therapy-naive HIV-infected (69.4% Male and 88.7% Black subjects (> 30 <50 years of age). The data revealed a significant (p=0.0005) decline in the % of OPG producing T cells in HIV-infected individuals, and a strong trend to increased T cell RANKL production (P=0.1). A significant negative association was found between the ratio of RANKL/OPG with T cell activation (CD69 expression) on CD4 (r=0.32, P=0.0008) and CD8 (r = 0.37, P<0.0001) T cells. In conclusion, our study shows that although B cells are the dominant source of basal OPG, T cells also contribute OPG under basal conditions and OPG production is reduced in HIV infection. Furthermore, a high proportion of activated T cells produce more RANKL in HIV infection leading to an increased RANKL/OPG ratio that may contribute to bone loss in HIV infected subjects.

#45 (morning session)

High throughput sequencing by pairing of B cell receptor's heavy and light chain (VH-VL) for analyzing SLE B cell subsets

Tomar D, Jenks S, Tipton C, Sanz I

Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease in which faulty B cell tolerance promotes multiple autoantibodies including some like anti-ds DNA, anti-Smith, and anti-nucleosome Abs with high disease specificity. In-depth analysis of the molecular and antigenic properties of antibody secreting cells (ASC) is critical for our understanding of SLE. However, low throughput methodologies to interrogate the B cells at single cell levels have hampered this goal. 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 various B cell populations from SLE patients. Traditional methods 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 10^6 B cells per experiment can be analyzed by this single-cell, emulsion-based technology for sequencing antibody VH-VL repertoires.

Methods: 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. Plasmablasts (CD19+IgD-CD27highCD38highCD138neg), switched memory (CD19+IgD-CD27+) and double negative (CD19+IgD-CD27-CXCR5-) B cells from SLE patients...
were flow sorted and VH and VL transcript were linked using emulsion RT-PCR. NGS was done on the IgH, IgL and linked transcripts on Illumina MiSeq.

Results: B cells for SLE patients showed highly polyclonal repertoire of all the B cell subsets analysed. However, significant clonal expansion in the antibody secreting cell compartments was also observed. High concordance was shown with Illumina miseq data obtained from bulk B cell subsets of the same blood draw. Both experiments also demonstrated the presence of substantial clonal expansions of the SLE-associated VH4-34 clones.

Conclusion: We have incorporated a high-throughput methodology of linking immunoglobulin heavy and light chain variable region (VH-VL) transcripts prior to amplification and repertoire analysis via NGS. 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.

#16 (afternoon session)

Gender differences in circulating progenitor cells and regenerative capacity
Topel ML, Ko YA, Hayek SS, Martin GS, Waller EK, Quyyumi AA

Introduction: Lower levels of circulating progenitor cells (PCs) confer reduced endogenous regenerative capacity and are associated with aging, subclinical vascular disease and mortality. Whether gender and menopause affect PC populations remains a subject of controversy.

Methods: 712 subjects (mean age 48, 65% female) were recruited from the Emory Predictive Health Study. Circulating levels of PCs were measured using flow cytometry of CD45med+ mononuclear cells co-expressing CD34 and its subset populations expressing CD133, CXCR4 and vascular endothelial growth factor receptor-2 (VEGFR2) epitopes. Testosterone and estradiol levels were measured for men and women, respectively.

Results: After adjustment for age, cardiovascular risk factors and body mass, CD34+ (β= -25%, P<0.001), CD34+/CD133+(β= -22%, P<0.001), CD34+/CXCR4+ (β= -25%, P<0.001) and CD34+/CXCR4+/CD133+ (β= -23%, P<0.001) PCs, but not VEGFR2+ PCs, were lower in women compared to men. Estradiol levels positively correlated with PC counts in women (P<0.05), but there was no association between testosterone levels and PC counts in men (P>0.05). In women, each 100% increase in estradiol was associated with an 11% (P=0.010) increase in CD34+, a 10% (P=0.027) increase in CD34+/CD133+, a 12% (P=0.011) increase in CD34+/CXCR4+ and a 12% (P=0.010) increase in CD34+/CXCR4+/CD133+ PCs after adjustment for risk factors, menopause and hormone replacement therapy.

Conclusion: Women have lower circulating PC counts compared to men. Estrogen levels were associated with PC levels in women. Since PCs are reflective of endogenous regenerative capacity, these findings may at least partly explain the rise in adverse cardiovascular events in women with aging and menopause.

#19 (morning session)

Cardiometabolic disease in high-incarceration neighborhoods
Topel ML, Kelli HM, Shen J, Martin GS, Quyyumi AA

Introduction: Over 20 million Americans are current or former prisoners, and the rate of incarceration is increasing. Blacks are imprisoned at rates 4 to 10 times greater than Whites. Although personal history of incarceration is associated with increased mortality and incident cardiovascular disease (CVD), the health impact of high incarceration rates in the community is unknown.

Methods: 1368 subjects from the Atlanta metropolitan area (mean age 49 ± 10 years, 62.1% female, 40.9% Black) were recruited from two community cohort studies. Subject zip codes were used to link neighborhood prison admission rates to individual-level risk factors for cardiometabolic disease.

Results: After controlling for demographics, neighborhood crime, body mass index and smoking, Black individuals living in areas with high prison admission rates were more likely to have metabolic syndrome (OR=2.05, 95% CI=1.19, 3.54), hypertension (OR=1.63, 95% CI=1.03, 2.58), dyslipidemia (OR=1.80, 95% CI=1.15, 2.83), impaired fasting glucose (OR=1.77, 95% CI=1.04, 3.03), elevated insulin (OR=2.52, 95% CI=1.43, 4.42) and elevated homeostatic model assessment for insulin resistance (OR=2.04, 95% CI=1.20, 3.47). There was no association between living in areas with high prison admission rates and cardiometabolic risk factors for White individuals.

Conclusion: Living in areas with high prison admission rates is associated with worse CVD risk profiles in Blacks, but not Whites. The community-level exposure of mass incarceration, particularly in Black communities, represents an additional health disparity that warrants further study in larger cohorts.

#26 (morning session)

Analysis of the dynamics of SICAVar gene expression in Plasmodium knowlesi malaria infections in silico reveals potential cellular mechanisms regulating antigen variability
Tseng CC, Chien JT, Lapp SA, MaHPIC Consortium, Galinski MR

One aspect of the malaria life cycle that has been a target of interest for antimalarial treatment and vaccine efforts is parasitic modification of the surface of infected erythrocytes.
with specific parasite-encoded antigens, which play a considerable role in malaria pathogenesis. In that context, this project focuses on variant expression of SICA (schizont-infected cell agglutination) antigens produced by Plasmodium knowlesi, a zoonotic parasite genetically related to the predominant human malaria parasite P. vivax. For P. knowlesi infected erythrocytes, variant expression of the SICAvar genes is dependent on the presence of a spleen. Using transcriptomic data collected from erythrocytes infected with P. knowlesi, a normalized time course of gene expression during P. knowlesi’s 24-hour life cycle was constructed utilizing a pipeline of RNA sequencing and bioinformatics approaches. A novel clustering strategy was then applied to group together P. knowlesi genes that share similar expression dynamics, with a consensus of the results revealing a subset of genes classified together with SICAvar, indicating likely co-expression. To more precisely identify the biological functions of these co-expressed genes, principal component analysis (PCA) was applied, and then Gene Ontology (GO) enrichment and metabolic pathway analysis on the different principal components. A unique set of cellular mechanisms were uncovered that may play a role in regulating SICAvar gene expression, including the production of distinct surface membrane components by the parasite. As a result, greater multifaceted insights may be revealed into underlying processes behind antigenic variation and the factors that may contribute to Plasmodium virulence.

#35 (afternoon session)

Non-encapsulated ST-11 *N. meningitidis* causing urethritis outbreak confers high level hetero-resistance to antimicrobial peptide polymyxin B


Historically, *Neisseria meningitidis* has not been considered a sexually transmitted pathogen. However, several outbreaks of ST-11 serogroup C invasive meningococcal disease among MSM populations and recently clusters of ST-11 meningococcal urethritis cases in heterosexual males have been documented. Thus, potentially through oral-genital contact, ST-11 N. meningitidis now appears capable of urogenital infection like *N. gonorrhoeae*. We provide molecular evidence indicating the recent urethritis outbreak in Columbus Ohio during 2015 is caused by a single capsule-defective meningococcal clonal strain belonging to the hyper-invasive ST-11 clonal complex (January - September 2015, n=52 unrelated cases). Insertion of IS1301 into the intergenic crs-css region of the cps locus results in deletion of capsule biosynthesis genes and loss of capsule expression, a genetic marker shared by all the Columbus urethral meningococcal outbreak isolates. Further, we found the meningococcal urethritis outbreak isolates demonstrated antimicrobial peptide polymyxin B resistance levels that are significantly greater than *N. gonorrhoeae* and exhibited the phenomenon of heteroresistance, subpopulations with further increased resistance to polymyxin B. This phenotype of heteroresistance is reported in *Neisseriae* for the first time. The unprecedented meningococcal urethritis outbreaks suggest that the ST-11 clone has evolved novel genetic and phenotypic changes in order to effectively colonize the urogenital tract, resist local innate immune responses and cause a sexually transmitted infection.

#44 (afternoon session)

Application of high-resolution metabolomics and text mining for acute respiratory distress syndrome

**Uppal K, Tran V, Jones DP, Li S, Esper A**

Specific at-risk diagnoses, such as sepsis, predispose to the development of the Acute Respiratory Distress Syndrome (ARDS); however, only 20-40% progress to ARDS and our ability to predict progression is poor. High-resolution mass spectrometers coupled with lipid chromatography can routinely measure several thousand chemical features in human samples. Plasmas samples and bronchoalveolar lavage fluid (BALF) were collected from a prospective cohort of 64 adult ICU patients meeting the ACCP/SCCM definition of severe sepsis or septic shock within 72 hours of sepsis development. Biological samples were extracted by acetoneitrile, and analyzed on a Thermo Q-Exactive Orbitrap mass spectrometer coupled with a reverse phase C18 column using positive electrospray ionization and a 10-min gradient. The metabolomics data were extracted and quantified using apLCMS and xMSanalyzer. Statistical analysis was performed using Wilcoxon ranksum test, linear regression, and sparse Partial least squares Discriminant Analysis. Pathway analysis was performed via mumichog. Literature-based discovery was performed using in-house text mining algorithms. High-resolution metabolomics analysis returned 6985 and 8694 metabolite features from plasma and BALF, respectively. The significant metabolites from plasma and BALF predicted ARDS at greater than 90% and 80% 10-fold cross-validation accuracy, respectively. The plasma metabolic pathways significantly associated with ARDS include glycerophospholipid metabolism, histidine metabolism, and glutamate metabolism. Text mining showed implicit and explicit relationships of ARDS with several biomedical entities including body organs, diseases/disorders, genes, metabolites, and enzymes. This study demonstrates the potential of high-resolution metabolomics and text-mining for identifying progression biomarker and understanding biological mechanisms in septic patients.

#17 (morning session)

Hospital discharge algorithm based on admission HbA1c for the management of patients with type 2 diabetes: sitagliptin discharge trial

**Urrutia MA, Anzola I, Gomez P, Oyedocum F, Vellanki P, Pasque F, Fayfman M, Umierrez GE**

Specific at-risk diagnoses, such as sepsis, predispose to the development of the Acute Respiratory Distress Syndrome (ARDS); however, only 20-40% progress to ARDS and our ability to predict progression is poor. High-resolution mass spectrometers coupled with lipid chromatography can routinely measure several thousand chemical features in human samples. Plasmas samples and bronchoalveolar lavage fluid (BALF) were collected from a prospective cohort of 64 adult ICU patients meeting the ACCP/SCCM definition of severe sepsis or septic shock within 72 hours of sepsis development. Biological samples were extracted by acetoneitrile, and analyzed on a Thermo Q-Exactive Orbitrap mass spectrometer coupled with a reverse phase C18 column using positive electrospray ionization and a 10-min gradient. The metabolomics data were extracted and quantified using apLCMS and xMSanalyzer. Statistical analysis was performed using Wilcoxon ranksum test, linear regression, and sparse Partial least squares Discriminant Analysis. Pathway analysis was performed via mumichog. Literature-based discovery was performed using in-house text mining algorithms. High-resolution metabolomics analysis returned 6985 and 8694 metabolite features from plasma and BALF, respectively. The significant metabolites from plasma and BALF predicted ARDS at greater than 90% and 80% 10-fold cross-validation accuracy, respectively. The plasma metabolic pathways significantly associated with ARDS include glycerophospholipid metabolism, histidine metabolism, and glutamate metabolism. Text mining showed implicit and explicit relationships of ARDS with several biomedical entities including body organs, diseases/disorders, genes, metabolites, and enzymes. This study demonstrates the potential of high-resolution metabolomics and text-mining for identifying progression biomarker and understanding biological mechanisms in septic patients.
This multicenter trial determined the efficacy and safety of a hospital discharge algorithm based on admission HbA1c to guide outpatient therapy in medicine and surgery patients with T2DM (n=255). Patients with HbA1c ≤7% (n=68) were discharged on oral antidiabetic agents (OAD) with sitagliptin/ metformin combination. Those with HbA1c between 7% and 9% (n=99) were discharged on metformin/sitagliptin plus glargine at 50% of the inpatient dose. Those with HbA1c >9% (n=87) were discharged on metformin/sitagliptin plus glargine at 80% of the inpatient dose, or on basal bolus regimen. The primary outcome was changes in HbA1C at 3 and 6 months. Admission HbA1c reduced from 8.70±2.32% to 7.31±1.48% at 3 months and to 7.32±1.68% at 6 months (both, p<0.001). Mean daily glucose decreased from 211.6±53.8 mg/dl at enrollment to 134.3±32.5 mg/dl and 133.4±39.8 mg/dl at 3 and 6 months, respectively (both p<0.001). Patients with HbA1c<7% had a change from 6.27±0.48% to 6.28±0.80% and 6.22±0.99% at 3 and 6 months. Patients with HbA1c 7-9% had a reduction from 8.04±0.65% to 7.29±1.1% and 7.34±1.27% (both p<0.001), and those with HbA1c>9% had a reduction from 11.35±1.71 to 7.98±1.75% and 8.02±2.01% at 3 and 6 months (both p<0.001). Hypoglycemia (<70 mg/dl) was 23.5% in HbA1c<7%, 23.2% in HbA1c 7-9%, and 26.4% in HbA1c>9% groups. BG<40 mg/dl was reported in <2% of patients. In summary, our HbA1c-based discharge algorithm with oral agents with or without basal insulin was found to be safe and effective to manage general medicine and surgical patients with T2DM.

Nox1 regulates polarity during cell migration

Valdivia A, Duran C, San Martin A

Nox1 activity is required for PDGF-induced cell migration. The polarized reorganization of actin filaments and microtubules within the cytoskeleton is essential for directional movement. We hypothesize that Nox1 is required for PDGF-induced cell polarization. Using live cell microscopy to track the migration of individual cells in the leading edge of the scratch-wound, we established that mouse embryonic fibroblasts (MEFs)-derived from Nox1 KO animals migrate significantly slower after PDGF stimulation when compared to wild type cells. This is accompanied by a significant reduction in polarized lamellipodia formation and an aberrant orientation of the microtubule-organizing center toward the wound area. In contrast, Golgi polarization, which is depending on actin, was not affected by the presence of Nox1. Regarding to the molecular mechanism, we found that Nox1 KO cells exhibit hyper-phosphorylation of the PKCz, a member of the PARD3 complex of cell polarity regulators. The phosphatase PP2A has been described to control the activity of the complex PARD3/PKCz. Interestingly, treatment with Okadaic acid, a PP2A inhibitor, recapitulates the phenotype of Nox1 KO in wild type cells. Together, our data indicate that Nox1 plays a key role in the establishment of cell polarity during migration possible by a mechanism that involves the regulation of microtubules by PP2A/Par3/PKcz.

The contours of “Here”: phenomenology of space for assisted living residents approaching end of life

Vandenberge AE, Ball M, Doyle P, Halpin SN, Kemp C, Quest T, Perkins M

The spatial extent of a person’s life has been observed to decrease with age, mobility loss, chronic illness, institutionalization, and end-of-life status. Assisted Living (AL) settings are both protected spaces with support for daily activities and porous spaces that retain the potential for accessing the larger community. However, little is known about how residents experience space in AL. As increasing numbers of Americans are living and dying in AL, we sought to understand how the phenomenology of space changes as residents approach end of life, defined broadly to include periods of decline associated with advanced age or chronic illness where timing of death is uncertain. We conducted an interpretive phenomenological analysis of field notes and the first 15 interviews at four diverse AL settings in a study supported by funding from the National Institute on Aging (1R01AG047408-01A1). Our sample ranged in age from 65 to 103 years (mean age 88), was racially mixed (8 white and 7 black residents), and was predominantly female (11 female, 4 male residents). Several themes were expressed by AL residents. First, space shrinks with decline, with resident rooms increasingly becoming the focus for visitation and social contact. Negatively, shrinking space has aspects of confinement and also vulnerability, as options diminish and privacy is compromised with more intense care. Positively, some residents speak of an intimacy of space within room settings. Understanding how both positive and negative phenomenological experiences operate as residents approach end of life can inform interventions to improve quality of dying in AL.

The utility of a multidisciplinary liver tumor clinic (MDTC) to treat patients with hepatocellular carcinoma (HCC) at a large volume liver transplant center


Background: HCC patients require coordinated care between multiple specialists. The MDTC at Emory utilizes a same-day, team-based approach to achieve an individualized treatment plan. Little evidence exists demonstrating benefit of MDTCs in clinical outcomes.

Methods: Patients seen at the MDTC with HCC between 1/2012 and 12/2015 were identified and compared to patients seen in general hepatology clinic (GHC) with incidentally diagnosed HCC during the study period. The outcomes studied were time to loco-regional therapy (LRT), time to transplantation, and 6- and 12-month survival.
Predictors of these outcomes were compared between cohorts using univariate regression.

Results: 245 patients were seen in the MDTC and 202 patients in GHC during the study period. In both clinics, the majority of patients were male, Caucasian, and hepatitis C was the primary etiology of liver disease. For cirrhotic patients with HCC who presented within Milan criteria, those seen in MDTC were more likely to undergo first LRT within 60 days (OR 1.8, p=0.028) compared to GHC patients. Age (OR 1.03, p=0.068) and MELD (OR 1.09, p=0.010) were also significant predictors of LRT within 60 days. MDTC vs GHC (OR 2.66, p=0.001) and age (OR 1.03, p=0.018) were significant predictors of transplantation within 150 days.

Conclusion: An MDTC for the treatment of HCC offers an efficient paradigm to optimize outcomes. Patients with HCC seen in the MDTC vs GHC were more likely to undergo LRT within 60 days and to be transplanted within 150 days, suggesting the potential of the MDTC model to improve patient outcomes.

#1 (afternoon session)

Colonoscopy procedural volume increases polyp detection rates in GI trainees: a longitudinal analysis

Vora R, Levy S, Qayed E

Purpose: Adenoma and polyp detection rates (ADR and PDR) are important measures of colonoscopy quality. It is assumed that ADR and PDR improve with increasing procedural volume. The goal of this study is to examine the change in ADR and PDR in individual GI fellows throughout their training.

Methods: Colonoscopies performed by fellows were reviewed from 7/1/09 to 7/1/14. Findings from screening colonoscopies were used to calculate ADR and PDR for each fellow for the previous 50 colonoscopies at each time point. ADR and PDRs were plotted against the total colonoscopy procedural volumes to produce longitudinal graphs. Models were controlled for patients’ mean age, percentage of male patients, and prep quality in the 50 procedures used to calculate ADR and PDR at each measurement time point.

Results: During this period, a total of 12 fellows who completed training and were included in the analysis. Longitudinal plots show that ADR and PDR increase for most fellows with increased procedural volumes. There is an overall increase in ADR and PDR throughout fellowship training. The average ADR at the first measurement occasion was 31.5%. There was statistically significant increase in ADR with increasing procedural volume (1.7% ± 0.4% per 100 colonoscopy, p=0.0026). There was statistically significant increase in PDR with increasing procedural volume (2.8% ± 0.5% per 100 colonoscopy, p=0.0002).

Conclusion: In this longitudinal analysis, there was a statistically significant increase in ADR and PDR with increased procedural volume during training. This highlights the importance of achieving adequate colonoscopy procedural volumes during training.

#60 (morning session)

Changes in the ubiquitin proteasome system in pulmonary hypertension

Wade BE, Deng Q, Zhao J, Ma J, Hart CM, Sutliff RL

Pulmonary Hypertension (PH) entails the sustained increase in pulmonary arterial pressure. Increased pulmonary vascular pressure and resistance result in right ventricular (RV) hypertrophy and can ultimately lead to RV failure and death. The mechanisms leading to vascular cell proliferation and vascular remodeling in PH are incompletely defined. Current therapeutic approaches address vasodilation 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 an important role in cellular homeostasis by regulating protein stability. Current evidence demonstrates changes in UPS activity in PH; however, the pathways and proteins influenced by these changes are poorly defined. Mice exposed to normoxic or hypoxic conditions for 3 weeks were used to identify proteins with altered ubiquitination in response to hypoxia exposure. Lungs were collected and the PTMScan® Ubiquitin Remnant Motif (K-ε-GG) Kit was used to precipitate ubiquitinated proteins for analysis by mass spectrometry (MS). 198 uniquely modified peptides were identified with a fold change ≥±1.5. In silico analysis revealed that these proteins are involved in 19 biological processes, 9 cellular compartments, and 3 molecular functions, several of which are important for cell proliferation, cell death, and cell cycle progression. These results using MS and in silico analysis suggest that hypoxia-induced changes in the UPS may significantly impact pathways that regulate cellular proliferation. These findings suggest several novel mediators of cell proliferation in PH for future study.

#50 (morning session)

The anti-CD38 monoclonal antibody TAK-079 depletes antibody secreting cells from normal and SLE patients


Background: Systemic lupus erythematosus (SLE) is characterized by expanded antibody secreting cells (ASCs) and the production of a variety of autoantibodies. Depletion of B cells by the anti-CD20 monoclonal antibody, Rituximab, has been widely used in autoimmune disease therapy. However, ASCs express low levels of CD20 and are poorly targeted. In this study, we examined the ability of TAK-079,
a monoclonal against CD38 which is expressed at high levels by ASCs, to inhibit antibody production.

Methods: TAK-079 was provided by Takeda California, in collaboration with XOMA Corporation. The depletion of ASCs from HC or SLE patients were determined by both flow cytometry and Elispot assay.

Results: The addition of TAK-079 in vitro depleted 80% of ASCs, by using flow cytometry. ASCs measured directly by Elispot were also reduced in both HC and SLE patient samples, that there was 70% reduction in the number of ASCs following TAK-079 treatment. Additionally, the number of cells producing autoantigen specific antibodies was dramatically reduced, including: VH4-34 9G4+ antibodies, anti-Ro, and anti-dsDNA. We elucidated the mechanism of plasma cell depletion and found that purified B cells alone were unaffected by TAK-079 mAb, whereas addition of NK cells elicited TAK-079 dependent depletion of ASCs.

Conclusion: Our results highlight the potential of TAK-079 monoclonal antibody for treating SLE via plasma cell depletion. By targeting CD38, TAK-079 effectively depleted both short lived and long-lived ASCs. Furthermore SLE ASCs producing antibodies against self-antigens were also efficiently depleted through NK cell and TAK-079 mediated ADCC in vitro.

#17 (afternoon session)

Yttrium-90 (90Y) radioembolization in the treatment of intrahepatic cholangiocarcinoma (ICC): preprocedural biomarkers of response

Wang XJ, Pillai AA, Kies DD, Camacho JC

A single center case-study evaluated 54 consecutive patients with unresectable intrahepatic cholangiocarcinoma who underwent 90Y radioembolization with either resin-based or glass-based spheres to identify preprocedural biomarkers of improved survival. Efficacy was assessed by overall survival (OS) from 90Y therapy. Prognostic factors were tested using univariable cox regression analysis including comorbid conditions, time to treatment, shunt fraction, type of 90Y, ECOG status, administered 90Y dose, tumor size, vascular involvement, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio. Multivariate analysis was then performed on any significant factors on univariate analysis in addition to several factors determined a priori. A total of 54 patients were identified (44% were male (n = 22), mean age 64 years old). 28% of patients underwent treatment with glass-based spheres (n=14) and 72% received resin-based spheres (n=36). Mean OS from diagnosis was 21.3 months (95% CI 18.0-35.0) and mean OS from treatment was 12.7 months (95% CI 6.4-20.9). No significant difference in OS between the two types of 90Y spheres for OS from diagnosis (HR 1.4, p=0.15) or OS from treatment (HR1, p = 0.99). Pre-identified biomarkers did not reach significance in univariate analysis for predicting survival. Hypertension showed an odds ratio (OR) of 0.47 (p =0.025) for survival from treatment. Time from diagnosis to 90Y therapy showed trend to significance with OR of 1.45 (p=0.058) for progression free survival. Multivariate analysis showed a trend for neutrophil/lymphocyte (N/L) ratio (HR 1.24 (0.99-1.55), p= 0.066) as predictor of survival.

#59 (afternoon session)

ZBTB46 deficiency may reduce the atheroprotective role of shear stress

Wang Y, Sun H, Rezvan A

Background: ZBTB46 is expressed in endothelial cells (ECs) and down-regulated by disturbed flow. Over expression of ZBTB46 in ECs keeps them quiescent and less proliferative. Here we explore the role of ZBTB46 in the development of atherosclerosis in response to shear stress. We hypothesize that ZBTB46 deficiency leads to EC activation and predisposes mice to atherosclerosis.

Methods: ZBTB46 wild type (zbtb46+/+) and global deficient (zbtb46-/-) mice, 8 weeks of age were injected a single dose of AAV-PCSK9 through tail vain to induce hypercholesterolemia. Mice were then subjected to left common carotid artery (LCA) partial ligation to induce disturbed flow within LCA, while the right common carotid artery (RCA) was used as control. At 2 weeks after ligation, mice carotids were harvested in formalin and atherosclerosis was quantified using Image J.

Results: At 2 weeks, WT mice developed mild atherosclerosis in LCA (%plaque area ± SEM: %23.14 ± 8.59) and very little plaque in RCA (%0.04 ± 0.02). zbtb46-/- mice also developed mild atherosclerosis in LCA (%11.72 ± 4.42) which was not statistically different compared to WT (p=0.29), but slightly more plaque in RCA (%0.17 ± 0.04, p=0.04).

Conclusion: ZBTB46 deficiency appears to have no effect on atherosclerosis at sites of disturbed flow probably attributed to the already low level of ZBTB46, but may promote atherosclerosis at sites of laminar shear. As ZBTB46 is also expressed in dendritic cells which are known to have an effect on atherosclerosis, future studies will include using EC specific KO mice and transgenic mice overexpressing ZBTB46.

#62 (afternoon session)

Angiotensin II-induced hypertension, inflammation and cardiovascular dysfunction: does SSH1L play a role?

Williams HC, Ma J, Weiss D, Taylor WR, Sutliff R, San Martin A

The dual specificity phosphatase Slingshot homolog 1 (SSH1L) contributes to actin remodeling by dephosphorylating and activating the actin-severing protein cofilin. Given that actin remodeling is implicated in hypertension, vascular stiffness, and inflammation, we
hypothese that SSH1 activity modulates angiotensin II (AngII)-induced hypertension and vascular inflammation. To investigate our hypothesis we generated SSH1−/− mice which display a significant increase in inactive/phosphorylated collagen in the aorta (0.42 +/- 0.08 AU vs. 1.77 +/- 0.18, p< 0.05 n= 5-8 mice per group) and have a modest increase in basal non-invasively detected systolic blood pressure (SBP) when compared to SSH1+/+ mice (108.40 +/- 1.97 v 101.40 +/- 2.46 mm Hg p< 0.05 n= 22-26). Nevertheless, chronic AngII treatment led to a similar increase in non-invasively detected SBP between both genotypes. When intravenously exposed to acute high-pressor doses of AngII SBP, diastolic blood pressure (DBP) and pulse pressure were equivalent between genotypes. However, SSH1−/− mice treated with vehicle (89.56 +/- 1.61 vs. 75.22 +/- 2.24 mm Hg p<0.05 n= 5-6 mice per group) or low-pressor doses of AngII (97.70 +/- 2.03 vs. 86.19 +/- 2.15 mmHg p<0.05 n= 5-6 mice per group) exhibit increased DBP compared to SSH1+/+ mice. In regards to AngII-induced inflammation, aortas of SSH1−/- mice infused with AngII for ten days exhibit increased osteopontin and TNFα mRNA transcripts when compared to SSH1+/+ mice. Taken together, our work indicates that pathways downstream of SSH1 modulate AngII-dependent pressor responses and inflammatory gene expression in the vasculature.

#64 (Morning session)

Racial differences in cerebral microcirculatory function and cognitive function
Wu J, Chand G, Sharma H, Qiu D, Hajjar I

Cerebrovascular reactivity (CVR), a measure of microcirculatory function in the brain, is impaired in hypertension and might be related to poor cognitive performance. African Americans (AA) are at double the risk of age-related cognitive decline. In this study, we aimed to evaluate racial differences in CVR and their associations with cognitive function in older adults with MCI and hypertension. This analysis was conducted on 70 patients (age=65.16 ±7.18; 38 females; 45 AA) in CALIBREX trial. All participants had their antihypertensive stopped, underwent cognitive assessment (MOCA=21.97 ±3.22) and a 6-minute blood oxygenation level-dependent (BOLD) imaging, with CO2 inhalation for 2 minutes. CVR was calculated as percentage augmentation between before and during CO2 inhalation. Associations with cognitive function (Trail-Making Test Part B (TMTB) and MOCA) were assessed using person’s correlation. Racial and gender differences were assessed using two-way ANOVA. AA had lower CVR in white matter (WM) in the frontal lobe (0.353% ±0.530%) than Caucasians (0.603% ±0.454%) (P=0.027). CVR values of grey matter (GM) (r=0.289, P=0.017) and WM (r=0.288, P=0.017) in the frontal lobe were associated with lower scores of TMTB, reflecting better performance on executive function. When stratified by race, Caucasians had a significant correlation in GM (r=0.445, P=0.026), while a trend toward significance in WM was observed among AA (r=-0.284, P=0.065). This study suggests that hypertensive AA have more impaired cerebral microcirculatory function. Our ongoing CALIBREX trial will provide evidence if antihypertensive therapy will be associated with both executive function and CVR improvement especially in AA.

#14 (morning session)

Risk of myocardial infarction among women versus men with nonobstructive left main coronary artery disease

Introduction: Nonobstructive (<49% stenosis) coronary artery disease (CAD) is more frequently detected in symptomatic women than men and is associated with increased myocardial infarction (MI) risk. However, nonobstructive CAD in the left main (LM) has not been previously assessed and sex-specific outcomes with nonobstructive LM are unknown.

Methods: In the multinational CONFIRM registry, patients with suspected, stable CAD underwent coronary computed tomographic angiography (CCTA) and were categorized as having no LM stenosis, nonobstructive LM, or obstructive LM. Kaplan-Meier and multivariable Cox analysis were used to assess sex-specific associations for LM strata and incident MI.

Results: Among 2,138 women and 4,134 men, the 5-year cumulative MI incidence among patients with no LM, nonobstructive LM, and obstructive LM, respectively, were 9%, 16%, and 26% for women (p<0.01) and 10%, 13%, and 21% for men (p<0.01). Compared to no LM, obstructive LM was strongly associated with MI in both women (adjusted HR 2.23, p=0.02) and men (adjusted HR 1.72, p=0.01). However, nonobstructive LM only increased MI risk in women (adjusted HR 1.68, p<0.01), but not in men (adjusted HR 1.18, p=0.16). Even among patients without any obstructive CAD, cumulative MI rates were higher in women with nonobstructive LM (p<0.01), but not in men (p=0.44). Importantly, nonobstructive LM doubled MI risk among women in this subset (adjusted HR 2.07, p=0.01), but did not increase risk among men (p=0.95).

Conclusion: Nonobstructive LM should be differentially highlighted among women as a high risk finding, potentially contributing to sex-related disparities among patients with nonobstructive CAD.
#25 (afternoon session)

Glucocorticoid-induced inhibition of AKT leads to phosphorylation of CREB via a PDE/cAMP/PKA pathway in skeletal muscle


Muscle atrophy in conditions like CKD and diabetes is associated with dysfunctional regulation of insulin/Akt/FoxO3 signaling. We recently found CREB, a transcription factor that regulates maintenance and regeneration of skeletal muscle, is phosphorylated in wasting conditions. This study investigated the mechanism that causes CREB phosphorylation under atrophic conditions induced by glucocorticoids. Differentiated C2C12 myotubes were treated with dexamethasone (Dex), LY294002 (PI-3 kinase inhibitor), H89 (protein kinase A inhibitor), IBMX (general phosphodiesterase (PDE) inhibitor), Milrinone (PDE3 inhibitor), or Rolipram (PDE4 inhibitor) for up to 6 h. Cells were harvested for Western blot analyses of phosphorylated and total CREB and AKT. Treatment of myotubes with 100nM Dex for 1-3 h inhibited Akt phosphorylation (pAkt). Dex treatment also increased CREB phosphorylation (pCREB) >170% within 3 h and it remained elevated for up to 12h. Inhibition of pAkt by LY294002 increased pCREB 400% over controls; treatment with LY294002 and Dex increased its level 170% over Dex alone. Since Akt can activate PDE3 and PDE4 and reduce cAMP/PKA signaling in non-muscle cells, we tested whether Dex-induced inhibition of PDE3/4 increases pCREB. Without Dex, general and PDE3/4 specific inhibitors increased pCREB by 370%, 324% and 360%, respectively. Finally, we tested whether inhibition of PKA by H89 prevents DEX-induced pCREB; H89 plus Dex attenuated pCREB to 46% of the control. Our study identifies a new mechanism by which atrophy-inducing conditions activate CREB. Inhibition of insulin/Akt signaling reduces the activity of PDE3/4. This leads to an increase in cAMP that activates PKA subsequent phosphorylation of CREB.

#52 (afternoon session)

The role of Poldip2/NOX4 in redox regulation of actin in integrin-mediated cell adhesion

Xu Q, Vukelic S, Seidel-Rogol B, Lassegue B, Griendling KK

Actin cytoskeleton assembly and organization, as a result of focal adhesion formation during cell adhesion, has been demonstrated to be highly related to reactive oxygen species (ROS) and cellular redox environment. Polymerase delta interacting protein 2 (Poldip2), a novel regulator of NOX4, plays a significant role in ROS production and cytoskeletal remodeling. Thus, we hypothesize that endogenous ROS derived from Poldip2/NOX4 contributes to redox regulation of actin and cytoskeleton assembly in integrin-mediated cell adhesion. Using vascular smooth muscle cells, we studied F-actin oxidation 30 min-6 h after cell attachment, a time of active integrin engagement. F-actin oxidation peaked at 3 h and was enhanced by overexpression of Poldip2. Depletion of Poldip2, or NOX4 expression using siRNA, or scavenging of endogenous H2O2 with catalase inhibited F-actin oxidation. To determine the consequence of F-actin oxidation, we examined the binding of F-actin to α-actinin, an actin binding protein that regulates branching. Wild-type actin interacted with α-actinin, but C285A and C374A redox-insensitive actin mutants led to disassembly of F actin and α-actinin. Silencing of Poldip2 also impaired actin-α-actinin interaction. These results suggest that integrin engagement during cell attachment activates Poldip2/NOX4 to oxidize actin and regulate cytoskeletal organization during cell adhesion.

#61 (morning session)

ESRD patients have altered pattern of heart rate variability responses to graded lower body negative pressure

Ye K, Downey RM, Liao P, DaCosta DR, Park J

End stage renal disease (ESRD) patients have autonomic neuropathy contributing to increased cardiovascular (CV) risk. Normal autonomic response to orthostatic stress is increased sympathetic nervous system (SNS) and decreased parasympathetic nervous system (PNS) activation to maintain blood pressure. Prior studies have shown that healthy humans have decreases in heart rate variability (HRV) following increased orthostatic stress induced by graded lower body negative pressure (LBNP) reflective of increased SNS and decreased PNS activation to the heart. Given that ESRD patients have autonomic neuropathy, we hypothesized that ESRD patients have lower baseline HRV, and an inability to adjust SNS and PNS activity following orthostatic stress. We measured continuous beat-to-beat blood pressure and ECG at baseline and during increasing doses of LBNP (-5, -10, -15, -20, -30, -40 mmHg) in ESRD and healthy controls. HRV was quantified as NN interval and SDNN, reflective of total autonomic activity, and RMSSD and pNN50, reflective of PNS activity. We observed baseline SDNN (p=0.001), RMSSD (p=0.004), and pNN50 (p=0.016) were significantly lower in ESRD patients versus controls, suggesting chronically high SNS and low PNS activity. The slopes of change in RMSSD and pNN50 with increasing LBNP were significantly different between ESRD and controls (p=0.004 and p<0.001, respectively). Whereas controls exhibited gradual decreases in RMSSD and pNN50 with increasing LBNP, these values remained constant in ESRD patients, suggesting ESRD patients are unable to adjust PNS activity in response to orthostatic stress. Failure to adjust autonomic responses to orthostatic stress may contribute to orthostatic intolerance and increased CV risk.
**#45 (afternoon session)**

Peroxisome proliferator-activated receptor gamma activation attenuates alcohol-induced alveolar macrophage mitochondrial derangements and phagocytic dysfunction via miR-92a/b up-regulation

*Yeligar SM, Harris FL, Brown LA, Hart CM*

Alcohol abuse increases risk of respiratory infections through enhanced oxidative stress and impaired alveolar macrophage (AM) phagocytic function. PPARγ ligands reduce lung oxidative stress through down-regulation of NADPH oxidase 4. We hypothesized that treatment with pioglitazone (PIO), a PPARγ ligand, would attenuate alcohol-induced AM dysfunction by down-regulating Nox4-related microRNAs and decreasing AM oxidative stress. AMs were obtained from the bronchoalveolar lavage fluid of C57BL/6J mice fed alcohol (20% w/v) in the drinking water for 12 wks ± PIO (10 mg/kg/day by oral gavage during week 12). In parallel, MH-S cells, a mouse AM cell line, were transfected ± 50 nM miR-92a/b mimics and treated ± 0.08% ethanol for 3 ± 10 μM PIO on day 3. Levels of miR-92a/b, which bind to the 3'UTR of Nox4 to decrease Nox4, were assessed by qRT-PCR. mRNA and protein expression of PPARγ and Nox4 were measured by qRT-PCR and western blot. Oxidative stress was measured with DCFH-DA and Amplex Red assays, and mitochondrial bioenergetics was determined using an extracellular flux analyzer. AM phagocytosis was evaluated by S. aureus internalization. In vivo and in vitro, ethanol: 1) decreased PPARγ and miR-92a/b expression, 2) increased Nox4 expression, 3) enhanced oxidative stress, 4) decreased mitochondrial oxygen consumption rate, and 5) impaired phagocytic capacity. miR-92a/b mimics or PIO treatment reversed these ethanol-induced AM derangements. Our studies suggest PIO is a clinically relevant intervention that will ameliorate alcohol-induced AM oxidative stress and dysfunction by up-regulating miR-92a/b despite continued alcohol ingestion.

**#53 (morning session)**

PTH induces bone anabolism through regulatory T cells

*Yu MC, Vaccaro C, Tyagi AM, Li JY, Hsu E, Steiner M, Adams J, Weitzmann MN, DiPaolo R and Pacifici R*

Intermittent PTH (iPTH) administration is the only FDA approved bone anabolic treatment for osteoporosis. T cells and their production of the Wnt ligand Wnt10b play a permissive role, but the mechanism by which iPTH regulates T cells and stimulates bone anabolism remains unknown. Here we show that in vivo iPTH treatment increases the differentiation of bone marrow (BM) conventional CD4+ cells into regulatory T cells (Tregs), causing a ~3-fold increase in the number of BM Tregs. Attesting to the relevance of Tregs, in vivo blockade of Treg expansion prevents iPTH induced bone anabolism and production of Wnt10b by BM CD8+ cells. Mechanistic studies revealed that iPTH activates NFAT1/2 and SMAD2/3 signaling leading to the binding of NFAT/SMAD complexes to a binding site critical for Wnt10b transcription located between -705 bp and -272 bp in the Wnt10b promoter. In vitro studies disclosed that PTH stimulates Wnt10b gene expression but only in conditions of blunted CD28 signaling. Confirming the critical role of CD28 signaling inhibition, iPTH treatment blunts CD28 signaling in CD8+ cells by downregulating CD80/86 expression in antigen presenting cells via Tregs. Therefore, expansion of Tregs is a critical, previously unknown mechanism by which iPTH exerts its bone anabolic activity.

**#63 (morning session)**

HIV-related proteins prolong macrophage survival through induction of Triggering receptor expressed on myeloid cells-1

*Yuan Z, Fan X, Staitieh B, Bedi C, Spearman P, Guidot DM, Sadikot RT*

Triggering receptor expressed on myeloid cells-1(TREM-1) is a member of the superimmunoglobulin receptor family. We have previously shown that TREM-1 prolongs survival of macrophages treated with lipopolysaccharide through Eg2-Bcl2 signaling. Recent studies suggest a role for TREM-1 in viral immunity. Human immunodeficiency virus-1 (HIV) targets the monocyte/macrophage lineage at varying stages of infection. Emerging data suggest that macrophages are key reservoirs for latent HIV even in individuals on antiretroviral therapy. Here, we investigated the potential role of TREM-1 in HIV latency in macrophages. Our data show that human macrophages infected with HIV show an increased expression of TREM-1. In parallel, direct exposure to the HIV-related proteins Tat or gp120 induces expression of TREM-1 in macrophages and confers anti-apoptotic attributes. RNA silencing of NF-kB p65 identified that these proteins induce TREM-1 in a NF-kB p65-dependent manner. TREM-1 Silencing in macrophages exposed to HIV-related proteins led to decreased expression of Bcl-2 and activation of caspase3, rendering them susceptible to apoptosis. These novel data reveal that TREM-1 may play a critical role in establishing HIV reservoir in macrophages by inhibiting apoptosis. Therefore, targeting TREM-1 could be a novel therapeutic approach to enhance clearance of the HIV reservoir, at least within the macrophage pools.

**#28 (morning session)**

The role of microRNA-26 on muscle-heart crosstalk in mice with chronic kidney disease


Exosomes, natural carriers of many signal molecules including microRNA (miR), mediate organ to organ communication. We hypothesized that miR-26 would benefit both CKD-induced muscle wasting and cardiomyopathy through exosome-mediated muscle-heart crosstalk. We found that serum-derived exosomes from CKD mice are larger than shams using NanoSight. MiR
Deep sequencing revealed increased miR-26a-5p in serum from both CKD mice and humans. However, miR-26a-5p was decreased in CKD mouse skeletal and cardiac muscle. Uremic serum enhanced secretion of miR-26a exosomes in cultured C2C12 skeletal and H9C2 cardiac muscle cells. We injected miR-26a-5p into tibialis anterior (TA) muscle and observed increased muscle cross-section area and decreased CKD-induced upregulation of atrogin-1 and MuRF1. We saw increased miR-26a expression in the heart following TA muscle injection. Interestingly, cardiac fibrosis was partially depressed in miR-26a overexpressing CKD mice. We further confirmed that FoxO1, α-SMA, GSK-3β, CTGF, fibronectin and Collagen1α were decreased by exogenous miR-26a in CKD mice. Cardiac sonography also showed that the percentage of ejection fraction was increased in CKD mice treated with miR-26a. In a cell culture model, we showed that exosomes containing miR-26a from skeletal muscle cells can transfer miR-26a to H9C2 cardiac cells and attenuate uremic serum-induced upregulation of FoxO1 in H9C2 cell, providing indirect evidence of skeletal and cardiac muscle crosstalk.

Conclusions: Exogenous miR26a not only attenuated skeletal muscle atrophy but also ameliorated uremic cardiomyopathy by targeting multiple mRNAs, possibly through exosome-mediated muscle-heart crosstalk.

#53 (afternoon session)

The involvement of ERK pathway in palmitate-induced ER stress and insulin resistance in skeletal muscles

Zhang P, Perry B, Xie Y, Espinoza D, Price SR

It is well-established that saturated fatty acids like palmitate cause metabolic dysfunction in skeletal muscles, including endoplasmic reticulum (ER) stress and insulin resistance. The signaling mechanisms that mediate these effects of palmitate on skeletal muscles are not well understood. We report that activation of the extracellular, signal-regulated kinase (ERK) pathway contributes to the rapid effects of palmitate on muscle cells in vitro. Time course analysis of ER stress markers (CHOP and ATF4) revealed that palmitate induces a dramatic increase in CHOP and ATF4 protein levels after 6h and the upregulation is sustained for at least 24 h. The ERK pathway is also activated within 12h treatment of palmitate, but returns to the control level after 24h of treatment of palmitate. To determine if the ERK pathway is necessary for the effects of palmitate on muscle cells, C2C12 myotubes were incubated for 12 h in the presence or absence (control) of 0.5 mmol/l palmitate and the ERK inhibitor U0126 (20 umol/l). Co-incubating myotubes with palmitate plus U0126 partially inhibits the palmitate-induced increase of CHOP and ATF4. Palmitate also suppresses insulin-induced AKT phosphorylation and inhibition of the ERK pathway with U0126 reverses the effect of palmitate on p-AKT. Taken together, these data indicate that ERK signaling is important for ER stress and insulin resistance induced by palmitate in muscle cells.
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Acknowledgements

We would like to thank all of our poster judges and abstract reviewers for their contributions to this event.

Planning Committee Members:
Madeleine Hackney, PhD, Faculty Chair
Alicia Lyle, PhD, Faculty Co-Chair
Kathy Griendling, PhD
Russ Price, PhD

Camille Vaughan, MD, MS
Ruxana Sadikot, MD
Colleen Kraft, MD, MS
Ashley Freeman

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