The Proceedings of the
15th Annual Research Day
Department of Medicine

May 1 & 2, 2017
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schedule of Events</td>
<td>3 - 4</td>
</tr>
<tr>
<td>Keynote Speaker: Tadataka Yamada, MD</td>
<td>5</td>
</tr>
<tr>
<td>Oral Presenters: May 1, 2017</td>
<td>6 - 25</td>
</tr>
<tr>
<td>Oral Presenters: May 2, 2017</td>
<td>26 - 41</td>
</tr>
<tr>
<td>List of Judges</td>
<td>42 - 44</td>
</tr>
<tr>
<td>Poser Author Index &amp; Abstracts: Residents - May 1, 2017</td>
<td>45 - 103</td>
</tr>
<tr>
<td>Poser Author Index &amp; Abstracts: Session A – May 2, 2017</td>
<td>104 - 204</td>
</tr>
<tr>
<td>Poser Author Index &amp; Abstracts: Session B – May 2, 2017</td>
<td>205 - 298</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>299</td>
</tr>
</tbody>
</table>
Schedule of Events

CLINICAL RESEARCH: RESIDENTS
MAY 1 - UNIVERSITY CLUB

5:00 pm  Registration & Poster Viewing

5:15 pm  Welcome & Opening Remarks

Mark Gladwin, MD
Chair, Department of Medicine
Director, Vascular Medicine Institute
Professor of Medicine, Division of PACCM

Alison Morris MD, MS
Vice Chair, Clinical Research
Professor of Medicine
Director, University of Pittsburgh HIV Lung Research Center
UPMC Chair, Translational Pulmonary and Critical Care Medicine

5:30-6:30 pm  Oral Presentations

Sokratis Apostolidis, MD
Emily Guhl, MD
Shelly Kakar, DO
Yijia Li, MD

6:30-7:30 pm  Poster Viewing Session & Discussion

7:30-8:00 pm  Keynote Speaker Introduction

Tadataka Yamada, MD
“An M.D. Degree – A Life Full of Options”
Venture Partner with Frazier Healthcare Partners

8:00 pm  Awards Presentation
<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 am</td>
<td>Registration &amp; Continental Breakfast Available</td>
</tr>
<tr>
<td>9:30-11:30 am</td>
<td>Session A: Poster Viewing &amp; Judging</td>
</tr>
<tr>
<td>11:30 am</td>
<td>Lunch Available</td>
</tr>
<tr>
<td>12:00-1:00 pm</td>
<td>Keynote Speaker</td>
</tr>
<tr>
<td></td>
<td><strong>Tadataka Yamada, MD</strong></td>
</tr>
<tr>
<td></td>
<td>&quot;Lessons from Global Health&quot;</td>
</tr>
<tr>
<td></td>
<td>Venture Partner with Frazier Healthcare Partners</td>
</tr>
<tr>
<td>1:15-3:15 pm</td>
<td>Session B: Poster Viewing &amp; Judging</td>
</tr>
<tr>
<td>3:30-4:30 pm</td>
<td>Oral Presentations</td>
</tr>
<tr>
<td></td>
<td><strong>Jill Allenbaugh, MD</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Neelesh Nadkarni, MD, PhD, FRCPC</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Natasha Parekh, MD</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Francois Yu, PhD</strong></td>
</tr>
<tr>
<td>4:30 pm</td>
<td>Awards Presentation</td>
</tr>
</tbody>
</table>
Keynote Speaker
Tadataka Yamada, MD

Dr. Tadataka Yamada is a Venture Partner with Frazier Healthcare Partners. Prior to joining Frazier he was Executive Vice-President, Chief Medical & Scientific Officer and a Board Member of Takeda Pharmaceuticals. Dr. Yamada has served as President of the Bill & Melinda Gates Foundation Global Health Program. In this position, he oversaw grants totaling more than $9 billion in programs directed at applying technologies to address major health challenges of the developing world including TB, HIV, malaria and other infectious diseases, malnutrition and maternal and child health. He was formerly Chairman, Research and Development and a Member of the Board of Directors of GlaxoSmithKline and before that he was Chair of the Department of Internal Medicine and Physician-in-Chief at the University of Michigan Medical Center.

Dr. Yamada holds a bachelor’s degree in history from Stanford University and obtained his M.D. from New York University School of Medicine. In recognition of his contributions to medicine and science he has been elected to membership in the National Academy of Medicine (US), the Academy of Medical Sciences (UK) and the National Academy of Medicine (Mexico) and he has received an honorary appointment as Knight Commander of the Most Excellent Order of the British Empire (KBE). He is a Past-President of the Association of American Physicians and of the American Gastroenterological Association and he has served as a member of the President’s Council of Advisors on Science and Technology and the Advisory Committee to the Director of the National Institutes of Health. He is currently Vice Chair of the Council of the National Academy of Medicine and serves on the Board of Directors of the Clinton Health Access Initiative.
Oral Presenter – May 1, 2017
Sokratis Apostolidis, MD
Resident - International Scholar

Bio: Sokratis is a PGY-2 Internal Medicine resident in the IST scholars’ track of the UPMC Internal Medicine Residency program. He was born and raised in Greece and completed his medical school studies in the University of Athens. Halfway through his medical training, he became drawn to immunology and rheumatologic diseases and shortly after his graduation, he joined the Rheumatology Lab of Dr. Tsokos in Beth Israel Deaconess Medical Center. As a post-doctoral fellow in Boston, he performed research on lupus nephritis and the role of the Protein Phosphatase 2a in Systemic Lupus Erythematosus pathogenesis. His research work on autoimmunity and immune tolerance has been published in the Journal of Immunology, Journal of Biological Chemistry and Nature Immunology. During his internal medicine residency, his research interests focus on identifying the underlying mechanisms contributing to vascular injury in scleroderma patients.

Presentation: Single cell RNA sequencing reveals a signature of endothelial injury in scleroderma skin.

Background: Vascular injury is a hallmark event in the pathogenesis of Systemic Sclerosis (SSc). Endothelial dysfunction happens early in the course of the disease and drives some of the most prominent clinical manifestations of scleroderma, including Raynaud’s phenomenon, telangiectasias and gastric antral vascular ectasias, pulmonary arterial hypertension and scleroderma renal crisis. The exact mechanisms that lead to endothelial cell injury and propagate the vasculopathy in scleroderma are not well understood. Single cell RNA sequencing provides a robust platform for cellular identification, allows gene expression analysis at the single cell level and accounts for cellular heterogeneity.

Methods: The study was completed in the Scleroderma Center of UPMC in collaboration with the Boston University Scleroderma Center and the Broad Institute of Boston. Scleroderma patients and healthy matched controls at UPMC and Boston University Scleroderma Centers were
recruited. Skin biopsies were obtained and the tissues were digested to form single cell suspensions. We then implemented single cell FACS-sorting and subsequent RNA sequencing of the isolated cells from scleroderma and healthy control skin. The analysis was performed using R software. We used t-distributed stochastic neighbor embedding (t-SNE) with k-means clustering to identify the various cell types. We performed pathway analysis using Gene Set Enrichment Analysis (GSEA) and Ingenuity Pathway Analysis (IPA). Finally, we independently verified distinct markers using immunohistochemistry on skin biopsies and qPCR in primary endothelial cells isolated from skin of scleroderma patients and healthy controls.

Results: In order to be able to visualize and ultimately define the various cell subsets in the dataset, we used t-distributed stochastic neighbor embedding (t-SNE), a method of unsupervised learning for dimensionality reduction. 2D projection of the t-SNE coupled with k-means clustering effectively reduced the dimensionality of the data revealing clustering patterns that had the potential to represent distinct cellular populations, as shown in Figure 1.

Figure 1.

2D t-SNE projection
The purpose of our analysis was to identify endothelial cells. In order to define the cluster that represents the endothelial cell population in our dataset, we employed known endothelial cell markers, such as Von Willebrand factor (gene name VWF), platelet endothelial cell adhesion molecule (gene name PECAM1) and vascular endothelial cadherin (CDH5). We overlaid the expression of these genes on the t-SNE projection plot and were able to positively identify the endothelial cells among the sorted single cells from healthy and scleroderma skin. Cluster 4 in Figure 1 is the cluster that represents the endothelial cells based on the expression of the abovementioned genes (the expression of the genes is not depicted in Figure 1).

After defining the endothelial cells in our dataset, we focused our analysis on the endothelial cell subpopulation and identified differentially expressed genes between healthy control ECs and SSc ECs. As it can be seen in Figure 2, the two fold upregulated genes (top bin) contains already established markers of endothelial injury and activation including the Apelin receptor APLNR and stabilin-1 (gene name STAB1), as well as previously identified markers of endothelial injury and negative regulation of angiogenesis in scleroderma, such as THBS1 and VWF. It also includes components of the extracellular matrix, such as the heparin sulfate proteoglycan 2 (gene name HSPG2) that was previously shown to be implicated in fibrotic processes including scleroderma-associated fibrosis, wound healing and to be regulated in a TGF-β dependent manner.

In order to highlight pathways that are enriched in our dataset and to find gene signatures that are positively or negatively regulated in scleroderma endothelial cells compared to their healthy counterparts, we used Gene Set Enrichment Analysis (GSEA) (45) and Ingenuity Pathway Analysis (IPA, Qiagen). Using GSEA we were able to demonstrate that the SSc endothelial cell expression profile is enriched in processes associated with extracellular matrix (ECM) generation as well as epithelial-to-mesenchymal transition (EMT). In addition, using Ingenuity Pathway, we found that scleroderma endothelial cells show enrichment in pathways associated with inhibition of angiogenesis, acute phase response, complement activation and matrix metalloproteinases (Figure 3).
Figure 2.
Finally, two of the top differentially expressed genes, HSPG2 and APLNR, were independently verified. Primary endothelial cells isolated from scleroderma skin expressed higher
levels of APLNR compared to endothelial cells isolated from healthy skin. HSPG2 showed increased expression in the perivascular area of scleroderma skin compared to healthy skin.

Conclusion: Using single cell RNA sequencing, we were able to identify an endothelial cell gene signature in scleroderma skin. Differential gene expression and pathway analysis revealed that endothelial cells from scleroderma patients exhibit a pattern of endothelial injury and activation as well as increased extracellular matrix generation and negative regulation of angiogenesis.

References
9. Kzhyschkowska J, Gratchev A, Goerdt S. Stabilin-1, a homeostatic scavenger receptor with


Oral Presenter – May 1, 2017

Emily Guhl, MD

Resident - Clinical Scientist

Bio: Emily Guhl is a third year resident in the Clinical Scientist Track of the internal medicine program at the University of Pittsburgh Medical Center. She completed her undergraduate degree in Biology at Washington University in St. Louis in 2010 and then went on to earn an M.D. from University of Chicago Pritzker school of medicine in 2014. Her research interests include social determinants of cardiovascular health, atrial fibrillation, and cryoablation for atrial fibrillation. Throughout her residency she has worked on various research projects under the mentorship of Dr. Sandeep Jain, Dr. Jared Magnani, and Dr. Bruce Rollman. She is excited to begin Cardiology Fellowship at the University of Pittsburgh Medical Center this July. In her spare time, Emily enjoys running with her dog Porter and participating in local kickball and dodgeball leagues.

Presentation: Getting by with a Little Help from my Friends: The Impact of Social Support on Depression, Quality of Life and Guideline-Recommended Medication Use in Patients with Heart Failure

Summary: Heart Failure (HF) is a highly prevalent disease with significant social, financial, and medical costs. It currently impacts ~6.5 million Americans with 960,000 newly diagnosed cases each year and >300,000 deaths. The total cost of HF in the United States is ~$30.7 billion annually. Individuals with HF who screen positive for depression have worse clinical outcomes including 12-month mortality rates. Higher levels of social support are associated with improved health outcomes and may mediate outcomes in individuals with depression. It is unclear if the relationship between social support and health outcomes is confounded by disease burden, adherence with guideline-recommended care, or other factors. Particularly, data examining the impact of perceived social support in individuals with systolic HF are limited.

Objectives: The objective of the current study is to evaluate the association of perceived level of social support on sociodemographic and clinical characteristics among hospitalized
patients with systolic HF (EF≤45%) using the Hopeful Heart Trial cohort.

The Hopeful Heart Trial: The individuals included in our analysis included the Hopeful Heart cohort. The Hopeful Heart Trial is an ongoing randomized controlled trial evaluating the impact of treatment of co-morbid depression in individuals with systolic HF. As part of the Hopeful Heart Trial, we screened patients with systolic HF and NYHA class II-IV symptoms for depression with the Patient Health Questionnaire (PHQ-2) at 8 Pittsburgh-area hospitals, prior to discharge home, and telephoned them two weeks later to administer the PHQ-9. Protocol-eligible patients had both: (1) a positive PHQ-2 depression screen and scored ≥10 on the PHQ-9 (“depressed”); or (2) a negative PHQ-2 depression screen and scored <5 on the follow-up PHQ-9 (“non-depressed”). We included individuals from both the depressed and non-depressed cohorts in our analysis on social support.

Methods: We combined the data of study patients from both the “depressed” and “non-depressed” cohorts of the Hopeful Heart trial. Perceived social support was measured at baseline in the study using the ENRICHD Social Support Instrument (ESSI) which has been previously well-validated. We classified the participants who scored in the top quartile as having a “top levels” of social support, and used student’s t-test or chi-square test, when appropriate, to compare this group to the combined other quartiles on a variety of sociodemographic and clinical characteristics we collected at baseline by patient self-report (age, race, gender, NYHA classification) and chart review (medical diagnoses, medication use, cardiac ejection fraction), or during the two-week call (mental and physical health-related quality of life (HRQoL): SF-12 MCS and PCS, respectively; mood: PHQ-9).

Results: We collected data from March 2014 to November 2016 from a total of 545 patients
with systolic HF. There were 178 patients assigned to our “High Social Support” group with an ESSI cut-off of ≥32. When we compared this group to our lower levels of social support, those who scored at the top level were more likely to be white (79% vs. 69%, p=0.02) and married (60% vs. 34%, p<0.001). The high social support group reported fewer mood symptoms (PHQ-9, mean score: 9.7 vs. 12.6, p<0.001) and higher levels of mental HRQoL (SF-12 MCS, mean score: 48.3 vs. 41.8, p<0.001). Finally, when looking at use of guideline-directed medical therapy they were more likely to be on a statin (73% vs. 63%, p = 0.02). Otherwise, the two groups were similar by age (mean: 63.6 years), gender (44% female), physical HRQOL (SF-12 PCS, mean: 31.3), medical comorbidity (50% DM, 83% HTN), EF (27.6%), NYHA class (II 40%, III 51%, IV 9%), use of ACE/ARB (59%), and beta-blockers (86%).

Table 1:

<table>
<thead>
<tr>
<th></th>
<th>High Social Support (top quartile) (N=178)</th>
<th>Other (lower 3 quartiles) (N=367)</th>
<th>P-value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>63.7 (13.8)</td>
<td>63.5 (12.7)</td>
<td>0.852 t</td>
</tr>
<tr>
<td>Female, % (N)</td>
<td>42 (74)</td>
<td>45 (164)</td>
<td>0.492 c</td>
</tr>
<tr>
<td>Race Group, % (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79 (140)</td>
<td>69 (252)</td>
<td>0.022 c</td>
</tr>
<tr>
<td>African American</td>
<td>19 (33)</td>
<td>29 (108)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (5)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, % (N)</td>
<td>83 (148)</td>
<td>83 (305)</td>
<td>0.849 c</td>
</tr>
<tr>
<td>Diabetes, % (N)</td>
<td>53 (94)</td>
<td>49 (181)</td>
<td>0.581 c</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, mean (SD)</td>
<td>7.4 (2.2)</td>
<td>7.6 (2.1)</td>
<td>0.389 t</td>
</tr>
<tr>
<td>Marital Status, % (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>16 (28)</td>
<td>26 (96)</td>
<td>&lt;.0001 c</td>
</tr>
<tr>
<td>Married</td>
<td>60 (106)</td>
<td>34 (124)</td>
<td></td>
</tr>
<tr>
<td>Sep/Div/Widowed</td>
<td>25 (44)</td>
<td>40 (145)</td>
<td></td>
</tr>
<tr>
<td>NYHA Class, % (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>43 (77)</td>
<td>38 (140)</td>
<td>0.424 c</td>
</tr>
<tr>
<td>III</td>
<td>47 (83)</td>
<td>53 (193)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>10 (18)</td>
<td>9 (34)</td>
<td></td>
</tr>
<tr>
<td>ESSI Score, mean (SD)</td>
<td>33.2 (0.9)</td>
<td>24.3 (5.7)</td>
<td>&lt;.0001 t</td>
</tr>
<tr>
<td>Aspirin, % (N)</td>
<td>74 (132)</td>
<td>67 (246)</td>
<td>0.091 c</td>
</tr>
<tr>
<td>ACE/ARB, % (N)</td>
<td>61 (108)</td>
<td>58 (214)</td>
<td>0.599 c</td>
</tr>
<tr>
<td>Statin, % (N)</td>
<td>73 (130)</td>
<td>63 (232)</td>
<td>0.023 c</td>
</tr>
<tr>
<td>Beta-Blocker, % (N)</td>
<td>84 (149)</td>
<td>87 (320)</td>
<td>0.271 c</td>
</tr>
<tr>
<td>Table:</td>
<td>Ejection Fraction, mean (SD)</td>
<td>28.5 (8.8)</td>
<td>27.1 (9.2)</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>PHQ-9, mean (SD)</td>
<td>9.7 (6.6)</td>
<td>12.6 (5.2)</td>
<td>&lt;.0001 t</td>
</tr>
<tr>
<td>PHQ-9 &gt;=10, % (N)</td>
<td>65 (115)</td>
<td>88 (322)</td>
<td>&lt;.0001 c</td>
</tr>
<tr>
<td>SF-12 MCS, mean (SD)</td>
<td>48.3 (13.7)</td>
<td>41.8 (11.9)</td>
<td>&lt;.0001 t</td>
</tr>
<tr>
<td>SF-12 PCS, mean (SD)</td>
<td>32.6 (11.5)</td>
<td>30.7 (10.1)</td>
<td>0.058 t</td>
</tr>
</tbody>
</table>

‡: c = Pearson’s Chi-Square Test   f = Fisher’s Exact Test   t = T-test

Note: Q1 is defined as anyone with ESSI total scores >=32 (75% or beyond) and Q2-Q4 is defined as anyone with ESSI total score <32 (less than 75%)

Limitations: Limitations of our study include that the Hopeful Heart Trial is still in progress and the study blind is scheduled to be removed in 2018; thus we are unable to evaluate clinical outcomes at this time. Additionally, given that we used depressed and non-depressed cohorts from the ongoing trial, patients with PHQ-9 scores in the mild symptom level (6-9) were not included. We also did not control for interactions between the different variables.

Conclusions: In patients with systolic HF, despite similar HF disease severity and medical burden, high-perceived levels of social support are associated with fewer mood symptoms and higher levels of mental HRQoL that may, in turn, translate to differences in clinical outcomes. Additionally, the patients with high perceived social support were more likely to be white, married, and on a statin. Upon opening our Trial’s study blind in 2018, future analyses will evaluate the impact of social support on clinical outcomes and use of guideline-recommended therapy.
Oral Presenter – May 1, 2017

Shelly Kakar, DO
Resident - Traditional Categorical

Bio: Shelly is a second year categorical Internal Medicine resident and plans to pursue a career in Gastroenterology and Hepatology. She is from Louisville, KY and was drawn to UPMC for the strong medicine department and unlimited resources for research. She graduated with her DO from the West Virginia School of Osteopathic Medicine, MS and BS in Physiology and Biophysics from the University of Louisville. On her free time she enjoys exploring Pittsburgh, working out, and spending time with friends and family.

Presentation: "Liver Transplant Outcomes: The Incidence of Renal Insufficiency in the NASH population"

Summary: Nonalcoholic Steatohepatitis (NASH) Cirrhosis is now the 2nd most common indication for liver transplantation (LT) in the United States and will likely surpass Hepatitis C as the number one cause in the next decade. The rising prevalence of obesity, diabetes mellitus, hypertension, and hyperlipidemia are important risk factors for the development of NASH. The development of chronic renal insufficiency (CRI) post LT is a well-known complication and has been associated with 4.5 fold-increased risk for mortality. A rate of 41.3% has been reported with a mean follow up of 5 years. This population includes all major causes of cirrhosis: alcoholic liver disease, viral hepatitis, NASH, primary biliary cholangitis, and cryptogenic cirrhosis. Associated risk factors for the development of CRI include hypertension, diabetes mellitus, calcineurin inhibitors for immunosuppression, use of nephrotoxic agents, pre-LT CRI, and pre-LT hepatorenal syndrome (HRS). Specific outcomes for the NASH population post-LT renal insufficiency are not well reported. To date, this is the first study to look specifically at the NASH population and post-LT outcomes and risk factors for the development of CRI.

Objective: The aim of the current study was to determine the incidence, risk factors and outcomes for the development of moderate to severe chronic renal insufficiency (CRI) in NASH
patients undergoing LT.

Methods: We utilized a prospectively collected database of a retrospective cohort of biopsy-confirmed NASH patients undergoing LT at the University of Pittsburgh Medical Center from 2000-2015. Demographic variables and outcomes were noted. Moderate to severe CRI was defined as a GFR of ≤ 44 mL/min per 1.73 m² (G3b per 'Kidney Disease Improving Global Outcomes'; KDIGO) for 3 months or greater, or those patients who became dependent on hemodialysis. The eGFR was calculated using CKD-EPI Creatinine Equation (2009) to estimate GFR by NKF.

Results: A total of 188 patients who underwent LT for NASH cirrhosis were available for analysis. Mean follow up was ~ 7 years post LT. Greater than 80% of all patients were on FK based immunosuppression. Ninety-nine patients (53%) of patients developed CRI (GFR ≤ 44 mL/min per 1.73 m) at least 3 months post LT with 17 of these patients becoming dialysis dependent. Pre-LT renal insufficiency (creatinine > 1.5) was significantly associated with the development of moderate to severe CRI post LT. Higher BMI at the time of LT, pre-existing diabetes mellitus, and older donor age were significant risk factors for the development of moderate to severe CRI post LT. There was a trend towards female sex, pre-existing hypertension, older age at LT and longer cold ischemic time (CIT) being risk factors as well, but they did not reach statistical significance. The use of FK based immunosuppression was equal in both groups and therefore difficult to interpret. There was no difference in survival at five-year follow amongst the two groups.

Table 1: Baseline patient demographics

<table>
<thead>
<tr>
<th></th>
<th>Patients with GFR ≤ 44 ml/min per 1.73 m² (N= 99)</th>
<th>Patients without CRI (N= 89)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of transplant (years)</td>
<td>60</td>
<td>58</td>
<td>0.15</td>
</tr>
<tr>
<td>Pre-LT Renal Insufficiency (Cr &gt; 1.5)</td>
<td>46</td>
<td>18</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>58%</td>
<td>44%</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI at time of transplant (kg/m²)</td>
<td>33</td>
<td>31</td>
<td>0.02</td>
</tr>
<tr>
<td>Donor Age (years)</td>
<td>62</td>
<td>48</td>
<td>0.11</td>
</tr>
<tr>
<td>Donor BMI (kg/m²)</td>
<td>28</td>
<td>30</td>
<td>0.47</td>
</tr>
<tr>
<td>Cold Ischemic Time (minutes)</td>
<td>542</td>
<td>480</td>
<td>0.10</td>
</tr>
<tr>
<td>5 year survival</td>
<td>85%</td>
<td>84%</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Table 2: Comparison of risk factors associated with development of CRI.

<table>
<thead>
<tr>
<th></th>
<th>Patients without CRI N= 89</th>
<th>Patients with GFR ≤ 44 N= 99</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FK based immunosuppression (Tacrolimus)</td>
<td>71</td>
<td>69</td>
<td>0.11</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>45</td>
<td>66</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26</td>
<td>42</td>
<td>0.07</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8</td>
<td>14</td>
<td>0.29</td>
</tr>
<tr>
<td>CAD</td>
<td>7</td>
<td>12</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Conclusions: Fifty-three % of patients with NASH cirrhosis developed moderate to severe CRI post-LT. Pre- LT renal insufficiency, pre-LT diabetes mellitus, higher BMI, and older donor age were risk factors. The development of CRI did not affect five-year survival. Future investigations include comparison of immunosuppression regimens and their influence in CRI development and analyzing interventions on risk factors (tighter management of pre-existing conditions such as diabetes mellitus, renal insufficiency, and hypertension) in the hopes of improving long-term renal function in this cohort of patients.

References:

Factors impacting progression of airway obstruction in HIV-infected individuals

Summary: In the era of antiretroviral therapy (ART), human immunodeficiency virus (HIV) has become a chronic disease, but mortality and morbidity associated with non-AIDS defining diseases has increased. It has been demonstrated that lung diseases, including chronic obstructive pulmonary disease (COPD), lung malignancy, pulmonary hypertension, and pulmonary fibrosis rates are significantly higher in the HIV-infected population compared with uninfected population, in both the pre-ART and ART eras [1]. Airflow obstruction as determined by decreases in the forced expiratory volume in one second (FEV1) is common in HIV-infected individuals and associated with increased respiratory symptoms and decreased six-minute walk distance. However, the trajectory of lung function decline as well as baseline characteristics associated with lung function decline remain largely unknown in this population. To assess progression of airflow obstruction over time, we utilized data from Pittsburgh HIV Lung Cohort to evaluate baseline characteristics that predicted with lung function decline in HIV-infected individuals.

Methods: The Pittsburgh HIV Lung Cohort is a multicenter cohort study established to evaluate pulmonary function in HIV-infected individuals. Participants were enrolled from Pittsburgh, PA and San Francisco, CA between 2007 and 2016. Inclusion criteria included HIV infection and age 18-80, with and without COPD diagnosis; exclusion criteria included pregnancy or breast-feeding, contraindication to pulmonary function testing, respiratory symptoms or fever within 4 weeks of study entry, hospitalization within 4 weeks of study entry, active cancer and infection. Pre- and post-bronchodilator pulmonary function testing was performed per American Thoracic Society guideline every 18 months [2]. We included data from study participants with at least three pulmonary function measurements to characterize the association between baseline characteristics and decline of post-bronchodilator forced expiratory volume in the first second (Post-BD FEV1) and Post-BD FEV1% predicted, which reflect the severity of airway obstruction.
Univariate analyses included age, sex, smoking history, illicit drug use, and baseline Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. We used a mixed effect linear model to evaluate factors associated with Post-BD FEV1\% decline and logistic regression model to evaluate factors associated with rapid Post-BD FEV1\% decline (defined as >80ml per year or >75th percentile based on the magnitude of annual decline in Post-BD FEV1 [3]).

Results: 272 HIV-infected participants were included (Table 1). Most participants were 40 to 50 years old, male (68.0\%), current (50.6\%) or former smoker (23.2\%), and had a history of marijuana use (82.5\%). The median duration of follow-up was 6.1 (IQR, 4.3-7.4) years. Median baseline CD4 cell count was 517 cells/µl (IQR 341-749), and 63\% had an undetectable HIV viral load at baseline. The majority (79.1\%) were on ART. Most participants (82.7\%) did not have a diagnosis of chronic obstructive pulmonary disease (COPD) at the time of enrollment, and median FEV1 \% predicted was 98\% (Table 1). Smoking history was significantly associated with baseline post-BD FEV1\% (>20 pack-year smoking history compared with non-smoker, difference -10.85\%, P<0.001) in univariate analysis (Table 2). Post-BD FEV1\% change rate was -1.2\% per year (IQR, -2.0\% - -0.4\%). Several factors were associated with faster Post-BD FEV1\% decline including age 51-60 years old compared with age 19-40 (-0.69\% per year, P=0.033) and baseline GOLD stage 1 compared with stage 0 (-1.01\% per year, P=0.006), while female sex (0.67\% per year, P=0.006) was associated with slower decline (Table 2). We also examined factors associated with rapid post-BD FEV1\% decline, defined as >80ml/year. In univariate analysis, female sex was a protective factor for rapid decline (OR 0.28, P<0.001). After adjusting for age and sex, smoking history (10-19.9 pack year compared with nonsmoker, OR 2.27, P=0.037) was the only significant factor associated with rapid decline (Table 3). Interestingly, after stratifying the analysis by baseline GOLD stage, higher baseline CD4 cell count (P-interaction=0.06) and ART use (P-interaction =0.17) at baseline were protective factors for rapid post-BD FEV1\% decline only in participants with GOLD stage 0 (Figure 1).
Table 1. Baseline characteristics of the cohort

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>272</td>
<td>47 (41-53)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>272</td>
<td>87 (32%)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>263</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack year</td>
<td>256</td>
<td>12.1 (0.0-26.8)</td>
</tr>
<tr>
<td>IDU, n (%)</td>
<td>263</td>
<td>54 (21%)</td>
</tr>
<tr>
<td>Marijuana, n (%)</td>
<td>263</td>
<td>217 (83%)</td>
</tr>
<tr>
<td>Crack cocaine, n (%)</td>
<td>251</td>
<td>102 (41%)</td>
</tr>
<tr>
<td>CD4 cell count (cells/μl)</td>
<td>269</td>
<td>517 (341-749)</td>
</tr>
<tr>
<td>VL detectable, n (%)</td>
<td>268</td>
<td>99 (37%)</td>
</tr>
<tr>
<td>On ART, n (%)</td>
<td>263</td>
<td>208 (79%)</td>
</tr>
<tr>
<td>Post-BD FEV1%</td>
<td>272</td>
<td>98 (86-110)</td>
</tr>
<tr>
<td>Post-BD FEV1 (L)</td>
<td>272</td>
<td>3.2 (2.7-4.0)</td>
</tr>
<tr>
<td>Post-BD FEV1/FVC</td>
<td>272</td>
<td>79 (74-84)</td>
</tr>
<tr>
<td>DLCO %</td>
<td>270</td>
<td>67 (57-76)</td>
</tr>
<tr>
<td>GOLD Stage</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>225 (83%)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>25 (9%)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>21 (8%)</td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>

Table 2. Baseline factors associated with Post-BD FEV1% change

<table>
<thead>
<tr>
<th></th>
<th>Effect on baseline FEV1%</th>
<th>Effect on annual rate of FEV1% change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-40</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>1.80 (-3.36 - 6.96)</td>
<td>0.5</td>
</tr>
<tr>
<td>51-60</td>
<td>-1.94 (-7.68 - 3.80)</td>
<td>0.5</td>
</tr>
<tr>
<td>60+</td>
<td>-1.15 (-9.95 - 7.65)</td>
<td>0.8</td>
</tr>
<tr>
<td>Female sex</td>
<td>-0.53 (-4.6 - 3.81)</td>
<td>0.8</td>
</tr>
<tr>
<td>Pack year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>0.1-9.9</td>
<td>-5.59 (-11.59 - 0.41)</td>
<td>0.07</td>
</tr>
<tr>
<td>10.0-19.9</td>
<td>-5.45 (-10.92 - 0.03)</td>
<td>0.051</td>
</tr>
<tr>
<td>≥20</td>
<td>-10.85 (-15.99 - -5.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>3.47 (-1.43 - 8.37)</td>
<td>0.17</td>
</tr>
<tr>
<td>Marijuana</td>
<td>0.93 (-4.37 - 6.22)</td>
<td>0.7</td>
</tr>
<tr>
<td>Crack cocaine</td>
<td>0.37 (-3.74 - 4.47)</td>
<td>0.9</td>
</tr>
<tr>
<td>CD4 cell count (per 10 cell/μl)</td>
<td>0.02 (-0.04 - 0.08)</td>
<td>0.5</td>
</tr>
<tr>
<td>HIV viral load detectable</td>
<td>-0.44 (-4.59 - 3.72)</td>
<td>0.8</td>
</tr>
<tr>
<td>On ART</td>
<td>-1.60 (-6.41 - 3.21)</td>
<td>0.5</td>
</tr>
<tr>
<td>GOLD stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-9.51 (-15.41 - -3.61)</td>
<td>0.002</td>
</tr>
<tr>
<td>2-3</td>
<td>-33.51 (-39.77 - -7.25)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Baseline factor associated with risk of FEV1 decline>80 ml/year (from baseline) in HIV-infected participants in the last follow-up visit.

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Age, gender adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-40</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>1.73 (0.89-3.37)</td>
<td>0.11</td>
</tr>
<tr>
<td>51-60</td>
<td>1.41 (0.67-2.95)</td>
<td>0.4</td>
</tr>
<tr>
<td>60+</td>
<td>2.38 (1.83-6.87)</td>
<td>0.11</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.28 (0.15-0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.37 (0.74-2.51)</td>
<td>0.3</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.98 (0.47-2.03)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pack year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>0.1-9.9</td>
<td>0.61 (0.25-1.44)</td>
<td>0.3</td>
</tr>
<tr>
<td>10.0-19.9</td>
<td>1.60 (0.79-3.24)</td>
<td>0.19</td>
</tr>
<tr>
<td>≥20</td>
<td>1.52 (0.78-2.96)</td>
<td>0.2</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>0.82 (0.44-1.55)</td>
<td>0.5</td>
</tr>
<tr>
<td>Marijuana</td>
<td>2.09 (1.01-4.33)</td>
<td>0.048</td>
</tr>
<tr>
<td>Crack cocaine</td>
<td>1.00 (0.59-1.69)</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>CD4 cell count (per 10 cell/μl)</td>
<td>1.00 (0.99-1.01)</td>
<td>0.5</td>
</tr>
<tr>
<td>HIV viral load detectable</td>
<td>0.92 (0.55-1.54)</td>
<td>0.8</td>
</tr>
<tr>
<td>On ART</td>
<td>0.93 (0.51-1.72)</td>
<td>0.8</td>
</tr>
<tr>
<td>GOLD Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.51 (0.65-3.49)</td>
<td>0.3</td>
</tr>
<tr>
<td>2-3</td>
<td>1.60 (0.66-3.87)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Figure 1. Higher CD4 cell count (A) and baseline ART use (B) are protective factors for rapid FEV1 decline only in HIV+ individuals who are GOLD stage 0 at baseline.

Conclusions: In this multicenter cohort study, we discovered that certain age group (51-60 years old), male sex and higher baseline GOLD stage were associated with more rapid Post-BD FEV1% decline. This study is one of the first large studies to examine progression of airway
obstruction in HIV. In terms of HIV-related factors, high CD4 cell count and ART use tended to be protective factor for rapid post-BD FEV1 decline only in HIV-infected individuals who were GOLD stage 0. This finding is consistent with a previous study showing that poorly controlled HIV is associated with accelerated lung function decline [4], although this study did not stratify their analysis by baseline pulmonary function. In contrary, the Strategic Timing of Antiretroviral Treatment (START) trial showed that timing of ART initiation based on CD4 cell count is not associated with lung function decline, but all individuals in this study initiated ART at a fairly high CD4 cell count level and prior to evidence of airway obstruction [5]. Further studies are warranted to evaluate the association between lung function decline and T cell subsets, as well as immune activation.

References:
Oral Presenter – May 2, 2017

Jill Allenbaugh, MD
Fellow – Medical Education Research

Bio: Jill Allenbaugh is a first year Academic Clinician Educator Scholars (ACES) Fellow in the department of general internal medicine. She received a BS in chemistry from Drexel University and spent two years working as a pharmaceutical chemist at GlaxoSmithKline before obtaining her MD at New York Medical College. She came to Pittsburgh for her residency in internal medicine which she completed in June 2016. She is currently working on a curriculum to enhance subspecialty teaching for internal medicine residents.

Presentation: "What did they say?" Teaching health literacy and communication skills to internal medicine residents to improve the patient experience"

Background: Residents are considered the frontline doctors on general medicine inpatient services as they are responsible for most direct patient communication. Our inpatient satisfaction surveys indicated there was room for improvement on the item, "My doctors explained things to me in a way that I could understand." We hypothesized the reasons for the communication gaps were residents’ lack of adequate training in bedside communication skills and difficulty in recognizing poor health literacy among inpatients. We also hypothesized that efforts aimed at clear communication can lead to improved patient care outcomes and satisfaction. Thus, we developed a curriculum for residents that focuses on effective tools for clear communication of medical information to patients on bedside rounds.

Methods: Participants included senior (N=112) internal medicine (IM) and internal medicine-pediatric residents at the University of Pittsburgh Medical Center. Residents attended a 3-hour workshop in June 2016 led by IM clinician educators which included didactics outlining clear communication techniques, small group discussion, role play, and video demonstration of simulated bedside rounding conversations. Residents who were unable to attend due to vacation or night float coverage received and reviewed the curricular materials electronically. Objective
communication skills on bedside rounds were assessed using a standardized skills checklist during a 3-month period before and after curriculum delivery. Knowledge and attitudes were assessed using pre- and post-tests. To assess attitudes, a Likert scale was used where 1=Not important and 5=Very important.

Results: 76/112 residents attended the workshop (participation 68%). Knowledge scores improved from 71.4% to 85.7% correct (p<.0001). Attitudes also improved, including the importance of translating medical information for patient care, mean pre 4.56 vs post 4.81, p=.0001) and for satisfaction (4.54 vs 4.81, p<.0001), introducing self and role (4.06 vs 4.56, p<.0001), and asking the patient “what questions do you have?” (4.82 vs 4.87, p<.0001). Three hundred thirty-three pre-and post-workshop observations of bedside rounds were collected. Observed communication skills significantly improved, including residents introducing themselves to the patient (49% vs 67%, p=.001), using plain medical language when giving medical information (89% vs 96%, p=.018), and asking “what questions do you have?” (16% vs 59%, p<.0001).

Table 1. Pre/Post survey of resident's perceived importance (N=72)

<table>
<thead>
<tr>
<th>Importance Items</th>
<th>Mean Pre</th>
<th>Mean Post</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Translating medical info for patient care</td>
<td>4.6</td>
<td>4.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Translating medical info for patient satisfaction</td>
<td>4.5</td>
<td>4.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Introducing yourself and team by name and role</td>
<td>4.1</td>
<td>4.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Asking “What questions do you have”</td>
<td>4.8</td>
<td>4.9</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Asking bedside nurse to add to presentation</td>
<td>4.4</td>
<td>4.6</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Table 2. Direct observation of communication skill at the bedside (N=205 pre) (N=168 post)

<table>
<thead>
<tr>
<th>Communication Skill</th>
<th>Pre (% done)</th>
<th>Post (% done)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The presenter and his/her title was introduced to the patient</td>
<td>48.6</td>
<td>66.7</td>
<td>0.001</td>
</tr>
<tr>
<td>The medical information was conveyed to the patient in plain nonmedical language</td>
<td>88.8</td>
<td>96.0</td>
<td>0.018</td>
</tr>
<tr>
<td>The team used the phrase &quot;what questions do you have?&quot;</td>
<td>16.3</td>
<td>59.4</td>
<td>.0001</td>
</tr>
<tr>
<td>Nurse was asked for updates or contributed voluntarily</td>
<td>47.5</td>
<td>48.7</td>
<td>0.835</td>
</tr>
</tbody>
</table>
Conclusion: Our results demonstrate that a small investment of curricular time devoted to health literacy and clear communication can significantly and objectively increase residents’ ability to translate medical information, and improve their knowledge and attitudes in these domains. This intervention can be readily disseminated to improve bedside patient communication and ultimately the patient experience.
Oral Presenter – May 2, 2017
Natasha Parekh, MD
Post-Doctoral Fellow – Health Services / Clinical Epidemiology

Bio: Natasha Parekh is a General Internal Medicine Clinical Research Fellow. She hails from Florida where she completed college and medical school at the University of Miami. She moved to Pittsburgh for her residency in Internal Medicine, and subsequently completed a chief residency year before starting her General Internal Medicine Fellowship. Her research has focused on women’s health issues and racial and ethnic disparities in Pennsylvania Medicaid. She looks forward to staying on as faculty next year in a job that combines clinical care with research on alternative healthcare delivery models at UPMC.

Presentation: Screening for Sexually Transmitted Infections After Medicaid Eligibility and Cervical Cancer Screening Guideline Changes

Background: Chlamydia and gonorrhea are the most commonly reported sexually transmitted infections (STIs) in the United States. STI screening is important to prevent complications like pelvic inflammatory disease and infertility, and is cost-effective. Major organizations therefore recommend annual screening in sexually active women <25 years old and older women at increased risk. From 2007-2013, Pennsylvania Medicaid began a family planning waiver which covered women’s health services (including STI testing) for uninsured women. Expectations were for STI screening to increase due to the program. However, national cervical cancer screening guideline changes in 2009 and 2012 recommended less frequent cervical cancer screening, causing concern that STI screening would decrease because the two screenings were typically performed concurrently (Figure 1). It is unclear how rates of STI screening changed in Pennsylvania Medicaid in response to these countervailing forces.
Methods: We performed an observational study evaluating medical claims for Medicaid-enrolled women 16-30 years of age from 2007-2013. We divided our population into 3 cohorts: 2007 (reflecting 2003 cervical cancer screening guidelines and start of the waiver program), 2010 (reflecting 2009 cervical cancer screening guidelines), and 2013 (reflecting 2012 cervical cancer screening guidelines). We required women to be continuously enrolled in Medicaid during their respective 1-year study period and that they had at least 1 outpatient visit to provide opportunity for screening. We excluded women who had HIV due to different screening recommendations and women were dually enrolled in Medicaid and Medicare. Our primary outcome was receipt of at least one STI test in the 1-year study period. We performed logistic regression to assess covariates associated with annual STI screening. Within-patient correlation was accounted for using robust standard error estimation. We accounted for We stratified regression results for all women, women <25 years, and women ≥25 y.

Results: Our sample included 506,520 person-years for 364,742 unique enrollees. Table 1
presents clinical characteristics of the population, stratified by time period (2007, 2010, 2013). There were 136,438 women in the 2007 period, 198,064 women in the 2010 period, and 172,018 women in the 2013 period. Mean ages were 22, 22, and 23 years in 2007, 2010, and 2013, respectively. The majority of the sample was white, non-Hispanic, and resided in an urban setting. Mean number of annual STI tests was 0.44, 0.71, and 0.70 in 2007, 2010, and 2013, respectively.

Table 1: Demographics, N= 506,520 person-years

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>2007 (n=136,438)</th>
<th>2010 (n=198,064)</th>
<th>2013 (n=172,018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (SD)</td>
<td>22 (4)</td>
<td>22 (4)</td>
<td>23 (4)</td>
</tr>
<tr>
<td>&lt;25 y.o.</td>
<td>94,841 (70)</td>
<td>139,329 (70)</td>
<td>115,211 (67)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78,272 (57)</td>
<td>118,147 (60)</td>
<td>97,947 (57)</td>
</tr>
<tr>
<td>Black</td>
<td>42,429 (31)</td>
<td>56,200 (28)</td>
<td>50,470 (29)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15,544 (11)</td>
<td>22,200 (11)</td>
<td>21,812 (13)</td>
</tr>
<tr>
<td>Enrolled in FP waiver</td>
<td>2 (0)**</td>
<td>37,047 (19)</td>
<td>35,326 (21)</td>
</tr>
<tr>
<td>Enrolled in MCO</td>
<td>111,120 (81)</td>
<td>147,342 (74)</td>
<td>157,496 (92)</td>
</tr>
<tr>
<td>Urban residence</td>
<td>123,730 (91)</td>
<td>178,228 (90)</td>
<td>156,335 (91)</td>
</tr>
<tr>
<td>Pap in time period</td>
<td>59,035 (43)</td>
<td>76,420 (39)</td>
<td>41,653 (24)</td>
</tr>
<tr>
<td>Contraception use</td>
<td>36,069 (26)</td>
<td>67,631 (34)</td>
<td>65,106 (38)</td>
</tr>
<tr>
<td>Pregnant</td>
<td>27,141 (20)</td>
<td>30,803 (16)</td>
<td>27,205 (16)</td>
</tr>
<tr>
<td>STI diagnosis or treatment</td>
<td>4,804 (3.5)</td>
<td>8,382 (4.2)</td>
<td>8,336 (4.9)</td>
</tr>
<tr>
<td>Sexually active</td>
<td>82,989 (61)</td>
<td>120,974 (61)</td>
<td>99,676 (58)</td>
</tr>
</tbody>
</table>

As shown in Figure 2, between 2007-2010, STI screening increased from 31% to 45%, and stabilized at 45% in 2013 for all women. STI screening was higher among sexually active women (defined by HEDIS® standards) compared with all women, but was similar between all women and those <25 years. STI screening significantly increased from 31% to 45% among all women, translating to a 45% increase from 2007 to 2010, and stabilized in 2013. Stratified by race and ethnicity, Blacks experienced 17-22% more STI screening than Whites and Hispanics experienced 3-6% more screening than non-Hispanics. Women enrolled in the family planning program experienced 5-6% more STI screening compared with women not enrolled in the program. Compared with women residing in non-urban areas, women residing in urban areas experienced 8-9% more STI screening.
As shown in Table 2, covariates significantly associated with receipt of annual STI screening included Black race (compared with Whites, AOR 2.56, 95% CI 2.54, 2.63), Hispanic ethnicity (compared with non-Hispanics, AOR 1.42, 95% CI 1.39, 1.46), and urban residence (compared with non-urban residence, AOR 1.17, 95% CI 1.13-1.22). Women enrolled in the family planning program were more likely to receive STI screening in all groups (AOR 1.42, 95% CI 1.39-1.46). Those receiving SSI were less likely to receive annual STI screening compared to other Medicaid eligibility groups (AOR 0.66, 95% CI 0.65-0.67).
Table 2: AOR (95% CI) for Risk Factors Associated with Annual STI Screening Using Multivariable Logistic Regression

<table>
<thead>
<tr>
<th>Covariate</th>
<th>All Women</th>
<th>&lt;25 y.o.</th>
<th>≥25 y.o</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group: 2010 vs. 2007</td>
<td>1.89 (1.86, 1.92)</td>
<td>1.89 (1.85, 1.92)</td>
<td>1.92 (1.86, 1.97)</td>
</tr>
<tr>
<td>2013 vs. 2007</td>
<td>1.75 (1.72, 1.78)</td>
<td>1.69 (1.66, 1.73)</td>
<td>1.97 (1.91, 2.02)</td>
</tr>
<tr>
<td>2013 vs. 2010</td>
<td>0.93 (0.92, 0.94)</td>
<td>0.90 (0.88, 0.91)</td>
<td>1.03 (1.00, 1.05)</td>
</tr>
<tr>
<td>Enrolled in FP Waiver</td>
<td>1.41 (1.38, 1.44)</td>
<td>1.37 (1.34, 1.41)</td>
<td>1.32 (1.28, 1.37)</td>
</tr>
<tr>
<td>Age, continuous</td>
<td>0.99 (0.99, 1.00)</td>
<td>1.07 (1.07, 1.08)</td>
<td>0.91 (0.91, 0.92)</td>
</tr>
<tr>
<td>Race, Blacks vs. Whites</td>
<td>2.56 (2.54, 2.63)</td>
<td>2.55 (2.51, 2.60)</td>
<td>2.68 (2.61, 2.75)</td>
</tr>
<tr>
<td>Ethnicity, Hispanics vs. non-Hispanics</td>
<td>1.42 (1.39, 1.46)</td>
<td>1.49 (1.44, 1.54)</td>
<td>1.32 (1.26, 1.39)</td>
</tr>
<tr>
<td>Enrolled in MCO</td>
<td>1.07 (1.05, 1.09)</td>
<td>1.06 (1.04, 1.08)</td>
<td>1.19 (1.15, 1.23)</td>
</tr>
<tr>
<td>Urban Residence</td>
<td>1.05 (1.03, 1.08)</td>
<td>1.01 (0.98, 1.03)</td>
<td>1.17 (1.12, 1.21)</td>
</tr>
<tr>
<td>Long-term care</td>
<td>0.80 (0.75, 0.84)</td>
<td>0.96 (0.91, 1.02)</td>
<td>0.24 (0.18, 0.31)</td>
</tr>
<tr>
<td>SSI</td>
<td>0.67 (0.66, 0.68)</td>
<td>0.69 (0.67, 0.70)</td>
<td>0.75 (0.73, 0.78)</td>
</tr>
<tr>
<td>Mental Health/Substance Use</td>
<td>0.98 (0.96, 0.99)</td>
<td>1.01 (0.99, 1.03)</td>
<td>0.92 (0.89, 0.94)</td>
</tr>
<tr>
<td>Visits</td>
<td>1.02 (1.02, 1.02)</td>
<td>1.02 (1.02, 1.02)</td>
<td>1.02 (1.02, 1.04)</td>
</tr>
<tr>
<td>Elixhauser</td>
<td>1.07 (1.06, 1.08)</td>
<td>1.08 (1.07, 1.09)</td>
<td>1.03 (1.02, 1.04)</td>
</tr>
</tbody>
</table>

Conclusion: We observed a dramatic increase in STI screening between 2007-2010. Potential reasons are the family planning waiver program (21% of our cohort was enrolled by 2013), increased use of urine and vaginal (rather than cervical) STI testing, electronic medical record alerts, and improvements in laboratory reporting. It is reassuring that despite clinician concerns, changes in cervical cancer screening guidelines did not affect STI screening. Between 2010-2013, screening stabilized at only 45%, suggesting opportunities for improvement.
Bio: Neelesh Nadkarni, MD, PhD, FRCPC, is Assistant Professor in the Division of Geriatric Medicine and Gerontology in the Department of Medicine, and a co-investigator in the Alzheimer’s Disease Research Center (ADRC) at the University of Pittsburgh. After graduating from JN Medical College, Karnatak University, India, he completed his residency in Internal Medicine at Crozer Chester Medical Center (Temple University), followed by three clinical fellowships - Geriatric Medicine at Northwestern Memorial Hospital (Northwestern University), Geriatric and Cognitive Neurology, and Hospital Medicine, both at Sunnybrook Health Sciences Center (University of Toronto, Canada). During his clinical fellowship at the University of Toronto he worked on his PhD examining gait, cognition and small-vessel disease in patients with Alzheimer’s disease. He was recruited as Pepper scholar to the University of Pittsburgh Pepper Center. He is a recipient of a K23 Career Development Award from the National Institute on Aging (NIH), and a New Investigator Award from the American Geriatrics Society. His research focuses on the influence of the age-related changes in the brain on the cognition-mobility interface in clinically normal older adults. His collaborations include departments within the School of Medicine, the Graduate School of Public Health and the School of Rehabilitation Sciences. His clinical work focuses on the Division’s in-patient and consult services at UPMC’s Presbyterian-Shadyside, Magee Women’s Hospital, and Mercy.

Presentation: **Prevalent and Incident Amyloid Positivity, and Relationship to Mild Cognitive Impairment (MCI) Outcome in Cognitively Normal Older Adults.**

Background: Amyloid plaques are one of the key pathological findings in the brain of individuals with Alzheimer’s disease (AD). Pittsburgh B (PiB)-PET, pioneered at the University of Pittsburgh, detects and quantifies fibrillar amyloid burden in the brain. Amyloid positivity on brain PiB-PET is an established antecedent biomarker of AD. Amyloid deposition in cognitively normal (CN) older adults starts in AD-signature regions, and spread to other regions, such that up to 30-55% of cognitively normal older adults over 70 years of age have globally high levels of amyloid in
the brain. Mild Cognitive Impairment (MCI), the earliest identifiable transitional phase that precedes clinical AD, is associated 10-15% conversion to clinical AD annually. While there is substantial evidence on the relationship between global amyloid positivity and MCI/AD in CN older adults there is comparatively less research on the relationship between regionally high amyloid levels and MCI outcomes in this population.

Methods: Community-dwelling elderly individuals (n=99) screened for psychiatric and neurologic conditions, were deemed CN based on their performance on standardized tests of memory, visuospatial construction, language, and attention and executive functions. Participants underwent PiB-PET scan at baseline, and a subset had repeat scans over subsequent 1-10 years (average follow-up: 4 years). PET methodology followed a standard procedure that involved the intravenous administration of [11C]PiB (15 mCi) followed by a 30 min PiB-PET study (6x300 sec frames) acquisition, 40-70 min post-injection. PiB standardized uptake value ratio (SUVR) was determined by normalizing each regional value to the cerebellar value. Each subject’s native PET and MR image data was co-registered using Statistical Parametric Mapping (SPM8) software. Each co-registered MR image was spatially normalized to an MR template and these transformation parameters were then applied to the parametric PET images and used for voxel-level group comparisons. Both the atrophy corrected and non-atrophy corrected and, regional and global PiB and FDG values will be analyzed. Participants were classified as amyloid positive, defined as regional PiB(+) (any one brain region-of-interest) and global PiB(+) (average of frontal, striatum, temporal, parietal, precuneus, cingulate brain regions-of-interest) using established PiB-PET cutoffs. Those not meeting the threshold of amyloid positivity on PiB-PET were classified as PiB(-). Imaging outcomes (stable PiB(-) or prevalent/incident regional PiB(+)) and clinical outcomes (stable cognitively normal or progression to MCI) were determined over the study period. Person-years in at-risk groups were calculated from baseline to 1st incident case (PiB(+)/MCI) or to final visit in non-incident cases (PiB(-)/CN). Annual incidence rates were derived by dividing the observed incidence by sum of person years. T-tests and Pearson’s chi-square were used for statistical analysis.

Results: In this sample of CN elderly individuals, mean (SD) age was 73.6 years (5.7 years), 64% were female, 21% were APOE-ε4 carriers and 83% white (Table 1).
There were no significant differences between the global PiB(+) and PiB(-) group on demographic measures and general cognitive performance measures. Regional PiB(+) participants were older (p=0.019), but were otherwise similar to PiB(-) participants.

Regional amyloid positivity was observed in 25 (25%) and global amyloid positivity was observed in 19 (18%). Annual incidence rates of regional amyloid positivity, regional-to-global amyloid positivity, and global amyloid positivity were 7%, 38%, and 5% respectively, while annual incidence rate of MCI was 7% (Table 2).

<table>
<thead>
<tr>
<th>Table 1: Sample characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=99</strong></td>
</tr>
<tr>
<td>Age (mean, range)</td>
</tr>
<tr>
<td>Gender (female, N, %)</td>
</tr>
<tr>
<td>Education (mean)</td>
</tr>
<tr>
<td>Race (White)</td>
</tr>
<tr>
<td>APOE-4 status (n=80)</td>
</tr>
<tr>
<td>Imaging follow-up duration (mean, range)</td>
</tr>
<tr>
<td>Clinical follow-up duration (mean, range)</td>
</tr>
<tr>
<td>MMSE score (mean, SD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2: Incident Amyloid positivity and MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline at-risk (N)</strong></td>
</tr>
<tr>
<td>Incident Regional Amyloid Positivity</td>
</tr>
<tr>
<td>Mean follow-up (years)</td>
</tr>
<tr>
<td>Person-years</td>
</tr>
<tr>
<td>Incident cases (N)</td>
</tr>
<tr>
<td>Annual Incidence rates</td>
</tr>
</tbody>
</table>
An amyloid positive PiB-PET at baseline or over the study period was associated with progression to MCI (OR=3.1 (95% CI: 1.2-8.2; p=0.02) and OR=4.6 (95% CI: 1.7-12.1, p=0.001 respectively).

**Conclusion:** Brain regional amyloid positivity heralds global amyloid positivity, and is associated with 5-fold increase odds of MCI in CN older adults. Prevalence and incidence of amyloid positivity in CN elderly individuals can inform the design of future secondary prevention trials targeting MCI and AD.
Oral Presenter – May 2, 2017
Francois Yu, PhD
Junior Faculty – Translational Research

Presentation: The Role of Nitric Oxide during Sonoreperfusion of Microvascular Obstruction

Background: Microembolization during PCI for acute myocardial infarction can cause microvascular obstruction (MVO). MVO severely limits the success of reperfusion therapies, is associated with additional myonecrosis, and is linked to worse prognosis, including death [1-3]. There is currently no consistently efficacious pharmacological approach for treating MVO. We have shown, both in in vitro and in vivo models, that ultrasound (US) and microbubble (MB) therapy (termed “sonoreperfusion” or “SRP”) is a theranostic approach that relieves MVO and restores perfusion in a rat hindlimb model [4], but the underlying mechanisms remain to be established.

Methods: We first demonstrated in plated cells that US-stimulated MB oscillations induced a 6-fold increase in endothelial nitric oxide synthase (eNOS) phosphorylation in vitro (Figure 1A and B). This increase required the presence of MB as US alone did not cause eNOS phosphorylation (Figure 1C).

Figure 1: In vitro eNOS phosphorylation: (A) Western blot of phospho-eNOS (S1177) and total-eNOS for Ionomycin (+ control), No Treatment (- control) and MB+US therapy; p-eNOS/t-eNOS ratio increased following MB+US therapy (n=3); (B,C) p-eNOS/t-eNOS ratio without MB did not induce eNOS phosphorylation (n=3) (* p<0.05).
We then monitored the kinetics of intramuscular NO and perfusion flow rate responses following 2-min of SRP therapy in the rat hindlimb muscle, with and without blockade of eNOS with LNAME. As expected, LNAME caused a sustained decrease in intramuscular NO (Figure 2A) over > 30 min. After a transient initial decrease, NO rose steadily following 2-min of SRP therapy and was significantly higher than at baseline starting 13 min after treatment. This increase was completely blunted with LNAME.

![Figure 2: (A) Intramuscular NO after LNAME injection (No US): Intramuscular NO level decreased steadily following i.v. LNAME injection at t=0 s in two rats, as expected; (B) Intramuscular NO following SRP in 4 rats with and without LNAME. (* p<0.05)](image)

Concomitantly, US contrast enhanced burst reperfusion imaging confirmed that there was a marked increase in perfusion flow rate at 6 and 10 min post SRP compared to baseline (>2.5 fold) (Figure 3). The increases in intramuscular NO and perfusion rate were blunted with LNAME.
Finally, we tested the hypothesis that NO plays a role in SRP by assessing reperfusion efficacy in a previously described rat hindlimb model of MVO during blockade of eNOS.
After US treatment 1, microvascular blood volume was restored to baseline in the MB+US group, but remained low in the LNAME group. Perfusion rates increased in the MB+US group after US treatment 2 but not in the MB+US+LNAME group.

Conclusions: These data strongly support that MB oscillations can activate the eNOS pathway leading to increased blood perfusion and NO plays a significant role in SRP efficacy.

References
Imad Al-Ghouleh  
Assistant Professor of Medicine  
Heart, Lung, Blood, and Vascular Medicine Institute, Division of Cardiology

Partha Sarathi Biswas, BVSc, MVSc, PhD  
Assistant Professor  
Division of Rheumatology and Clinical Immunology, UHCP-O-GME Residency

Sonya Borerro, MD, MS and Clinical and Translational Science, General  
Associate Professor of Medicine Internal Medicine  
Director, Center for Women’s Health Research and Innovation (CWHRI)  
Director, Career Education and Enhancement for Health Care Research Diversity (CEED)  
Program for Medical Students  
Co-Director, VA Advanced Fellowship Program in Women’s Health, VA Pittsburgh Healthcare System

Tullia Bruno, PhD  
Research Assistant Professor  
Department of Immunology

Stephen Chan, MD, PhD, FAHA  
Director, Center for Pulmonary Vascular Biology and Medicine  
Associate Professor of Medicine  
Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute  
Division of Cardiology, Department of Medicine

Neil Clancy, MD  
Associate Professor of Medicine, Division of Infectious Diseases  
Director, Mycology Program  
Chief, Infectious Diseases Section, VA Pittsburgh Health Care System

Jennifer Corbelli, MD, MS  
Assistant Professor of Medicine  
Division of General Internal Medicine  
Program Director, Internal Medicine Residency Training Program

Diwakar Davar, MD  
Assistant Professor of Medicine  
Division of Hematology/Oncology

Yohei Doi, MD, PhD  
Assistant Professor of Medicine, Division of Infectious Diseases  
Director, Center for Innovative Antimicrobial Therapy

Partha Dutta, DVM, PhD  
Assistant Professor of Medicine, Division of Cardiology

Michael Elnicki, MD  
Professor of Medicine  
Division of General Internal Medicine  
Director, International Medical Education Programs, UPSOM

Meghan Fitzpatrick, MD  
Instructor in Medicine  
Division of Pulmonary, Allergy and Critical Care Medicine

Michael Fine, MD, MSc  
Professor of Medicine, Division of General Internal Medicine  
Director, VA HSR&D Center for Health Equity Research and Promotion (CHERP)  
Director, Leadership and Discovery (LEAD) Program, Internal Medicine Residency Training Program  
Associate Director, Center for Research on Health Care (CRHC), University of Pittsburgh

Sarah Gaffen, PhD  
Gerald P. Rodnan Professor, Division of Rheumatology & Clinical Immunology  
Director, Basic Rheumatology Research

Walid Gellad, MD, MPH  
Associate Professor of Medicine, Division of General Internal Medicine  
Associate Professor of Health Policy and Management, School of Public Health  
Adjunct Scientist, RAND Corporation
Michael Jurczak, PhD
Assistant Professor of Medicine, Division of Endocrinology and Metabolism

Erin Kershaw, MD
Chief, Division of Endocrinology and Metabolism, Associate Professor of Medicine

Kevin Kraemer, MD, MSc
Professor of Medicine, and Clinical & Translational Science, Division of General Internal Medicine
Chief, Section of Treatment, Research, and Education in Addiction Medicine
Director, GIM Research Scholars Program
Co-Director, Clinical & Translational Science Fellowship
Co-Director, NRSA for Primary Medical Care

Janet S. Lee, MD
Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine
T1 Translational Track Director, Institute for Clinical Research Education
Member, Pittsburgh Heart, Lung, Blood and Vascular Medicine Institute

Burton Lee, MD, FCCP
Visiting Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
Internal Medicine Residency Program

David Levinthal, MD, PhD
Assistant Professor of Medicine
Division of Gastroenterology, Hepatology and Nutrition, Director, Neurogastroenterology & Motility Center

Bernard Macatangay, MD
Assistant Professor of Medicine, Division of Infectious Diseases
Assistant Director, University of Pittsburgh Immunology Specialty Lab (ACTG)

Mandy McGeachy, PhD
Assistant Professor of Medicine
Division of Rheumatology and Clinical Immunology

Bryan McVerry, MD
Assistant Professor of Medicine and Environmental and Occupational Health
Medical, Division of Pulmonary, Allergy, and Critical Care Medicine
Associate Director, Intensive Care Unit
Director, Translational Research in Acute Lung Injury, Director, Fellowship Program

Barbara Methé, PhD
Visiting Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine, Co-Director, Center for Medicine & the Microbiome

Ana Mora, MD
Associate Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine

Alison Morris, MD, MS
Professor of Medicine, Immunology and Clinical Translational Science
Director, Center for Medicine & the Microbiome, UPMC Chair of Translational Pulmonary and Critical Care Medicine
Vice Chair for Clinical Research, Department of Medicine

Suresh Mulukutla, MD
Assistant Professor of Medicine
Division of Cardiology

Seyed Nouraie, MD, PhD
Visiting Associate Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine

Enrico Novelli, MD, MS
Assistant Professor of Medicine, Division of Hematology-Oncology
Medical Director, UPMC Adult Sickle Cell Anemia Program
Associate Director, Hemophilia Center of Western PA
Bruce Rollman, MD, MPH  
Professor of Medicine, Psychiatry, Biomedical Informatics, and Clinical and Translational Science, UPMC Endowed Chair in General Internal Medicine

Marc Simon, MD, MS, FACC  
Associate Professor of Medicine, Bioengineering, and Clinical and Translational Research  
Director, Heart Failure Research/Clinical Hemodynamics Core Facility

Nicolas Sluis-Cremer, PhD  
Professor of Medicine  
Director of Laboratory Research, Division of Infectious Diseases

Carla Spagnoletti, MD, MS  
Associate Professor of Medicine, Division of General Internal Medicine  
Director, Academic Clinician-Educator Scholars (ACES) Fellowship in General Internal Medicine  
Director, Masters and Certificate Programs in Medical Education, Institute for Clinical Research Education, University of Pittsburgh

Cynthia St. Hilaire, PhD  
Assistant Professor of Medicine, Division of Cardiology

Arohan Subramanya, MD  
Assistant Professor of Medicine, Division of Renal-Electrolyte, Assistant Professor of Cell Biology and Physiology, Staff Physician, VA Pittsburgh Healthcare System, Graduate Faculty, Cell Biology and Molecular Physiology Program

Roderick Tan, MD, PhD  
Assistant Professor, Division of Renal-Electrolyte

Frederico G. S. Toledo, MD  
Associate Professor of Medicine  
Division of Endocrinology and Metabolism, Director of Clinical Research, Center for Metabolic and Mitochondrial Medicine

Liza Villanueva, MD  
Vice Chair of Pre-Clinical Research, Department of Medicine  
Professor of Medicine, Division of Cardiology  
Director, Non-Invasive Cardiovascular Imaging, Director, Center for Ultrasound Molecular Imaging and Therapeutics

Nathaniel Weathington, MD, PhD  
Assistant Professor of Medicine  
Division of Pulmonary, Allergy and Critical Care Medicine

Ora Weisz, PhD  
Professor, Department of Medicine, Divisions of Renal-Electrolyte and Cell Biology, Vice Chair of Faculty Development, Associate Dean for Faculty Development, Assistant Vice Chancellor for Faculty Excellence, Health Sciences

Dhiraj Yadav, MD, MPH  
Professor of Medicine, Division of Gastroenterology, Hepatology and Nutrition

Anna Zemke, MD, PhD  
Assistant Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine

Yutong Zhao, MD, PhD  
Associate Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care  
Associate Professor of Cell Biology  
Co-Director of Acute Lung Injury Center of Excellence
Residents

May 1, 2017
University Club, Ballroom B
<table>
<thead>
<tr>
<th>RESIDENTS</th>
<th>Name</th>
<th>Year-R</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajayi-Fox</td>
<td>Patricia</td>
<td>40-R</td>
<td>Perceptions of Strength of Social Support Amongst Patients with Decompensated Alcohol-related Cirrhosis</td>
</tr>
<tr>
<td>Arnold</td>
<td>Jonathan</td>
<td>4-R</td>
<td>Provider interest in lifestyle tracking within the EHR: data from the MAINTAIN-pc study</td>
</tr>
<tr>
<td>Bagenski</td>
<td>Amy</td>
<td>5-R</td>
<td>Effect of influenza vaccination in the severity of illness in hospitalized transplant recipients with laboratory-confirmed influenza</td>
</tr>
<tr>
<td>Bane</td>
<td>Nicole</td>
<td>6-R</td>
<td>Improving the Rate of Influenza and Pneumococcal Vaccination in a University-Based Teaching Clinic using a Simple Reminding System</td>
</tr>
<tr>
<td>Chen</td>
<td>Hui-Wei</td>
<td>7-R</td>
<td>Trajectory of Physical Performance Measured by Gait Speed Indicates Risk for Adverse Outcomes in Liver Transplant Candidates</td>
</tr>
<tr>
<td>Cheng</td>
<td>Debbie</td>
<td>8-R</td>
<td>Patterns between Multi-Year Steroid Use in Patients with Inflammatory Bowel Disease and Quality of Life, Disease Severity, Healthcare Utilization</td>
</tr>
<tr>
<td>Chin</td>
<td>David</td>
<td>46-R</td>
<td>Delicate Balance Inpatient vs. Outpatient: Resident Satisfaction Survey</td>
</tr>
<tr>
<td>Ertem</td>
<td>Furkan</td>
<td>10-R</td>
<td>What is the Expected Incidence of Interval Colorectal Cancer (CRC) for an Endoscopist in Active Clinical</td>
</tr>
<tr>
<td>Fox</td>
<td>Steven</td>
<td>41-R</td>
<td>Effects of Free Clinic Attendance and Continuity of Care on Emergency Department Visits</td>
</tr>
<tr>
<td>Gougol</td>
<td>Amir</td>
<td>11-R</td>
<td>Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experiences (APPRENTICE): An International Multicenter Consortium for the study of Acute Pancreatitis</td>
</tr>
<tr>
<td>Gougol</td>
<td>Amir</td>
<td>12-R</td>
<td>Association of Dietary Habits with Severe Acute Pancreatitis</td>
</tr>
<tr>
<td>Gougol</td>
<td>Amir</td>
<td>13-R</td>
<td>Clinical Outcomes of Isolated Renal Failure Compared to Other Forms of Organ Failure in Patients with Severe Acute Pancreatitis</td>
</tr>
<tr>
<td>Gougol</td>
<td>Amir</td>
<td>14-R</td>
<td>Different demographic, clinical and severity profile between patients with recurrent and first attack of acute pancreatitis (AP)</td>
</tr>
<tr>
<td>Gougol</td>
<td>Amir</td>
<td>15-R</td>
<td>Frequency and clinical predictors of pain and disability after 1 year of AP: A single center prospective study</td>
</tr>
<tr>
<td>Author</td>
<td>Last Name</td>
<td>First Name</td>
<td>Age</td>
</tr>
<tr>
<td>--------</td>
<td>-----------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Gougol</td>
<td>Amir</td>
<td></td>
<td>16-R</td>
</tr>
<tr>
<td>Guhl</td>
<td>Emily</td>
<td></td>
<td>17-R</td>
</tr>
<tr>
<td>Guhl</td>
<td>Emily</td>
<td></td>
<td>42-R</td>
</tr>
<tr>
<td>Jacobs</td>
<td>Zachary</td>
<td></td>
<td>47-R</td>
</tr>
<tr>
<td>Jacobs</td>
<td>Zachary</td>
<td></td>
<td>48-R</td>
</tr>
<tr>
<td>Jacobs</td>
<td>Zachary</td>
<td></td>
<td>49-R</td>
</tr>
<tr>
<td>Kakar</td>
<td>Shelly</td>
<td></td>
<td>18-R</td>
</tr>
<tr>
<td>Kennedy</td>
<td>Amy</td>
<td></td>
<td>50-R</td>
</tr>
<tr>
<td>Kensler</td>
<td>Caroline</td>
<td></td>
<td>43-R</td>
</tr>
<tr>
<td>Khalif</td>
<td>Adnan</td>
<td></td>
<td>19-R</td>
</tr>
<tr>
<td>Klein</td>
<td>Andrew</td>
<td></td>
<td>51-R</td>
</tr>
<tr>
<td>Koczo</td>
<td>Agnes</td>
<td></td>
<td>20-R</td>
</tr>
<tr>
<td>Kota</td>
<td>Karthik</td>
<td></td>
<td>21-R</td>
</tr>
<tr>
<td>Kota</td>
<td>Karthik</td>
<td></td>
<td>22-R</td>
</tr>
<tr>
<td>Name</td>
<td>First Name</td>
<td>Age</td>
<td>Resident Number</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>-----</td>
<td>-----------------</td>
</tr>
<tr>
<td>Kota</td>
<td>Karthik</td>
<td>23</td>
<td>R</td>
</tr>
<tr>
<td>Kurin</td>
<td>Michael</td>
<td>24</td>
<td>R</td>
</tr>
<tr>
<td>Li</td>
<td>Allen</td>
<td>25</td>
<td>R</td>
</tr>
<tr>
<td>Lu</td>
<td>Amy</td>
<td>52</td>
<td>R</td>
</tr>
<tr>
<td>Lucas</td>
<td>Aaron</td>
<td>1</td>
<td>R</td>
</tr>
<tr>
<td>Martinez</td>
<td>Silvia</td>
<td>26</td>
<td>R</td>
</tr>
<tr>
<td>Merkhofer</td>
<td>Cristina</td>
<td>27</td>
<td>R</td>
</tr>
<tr>
<td>Murali</td>
<td>Priyamvada</td>
<td>53</td>
<td>R</td>
</tr>
<tr>
<td>Nieves</td>
<td>Ricardo</td>
<td>28</td>
<td>R</td>
</tr>
<tr>
<td>Pacheco</td>
<td>Carlos</td>
<td>29</td>
<td>R</td>
</tr>
<tr>
<td>Parekh</td>
<td>Shrina</td>
<td>30</td>
<td>R</td>
</tr>
<tr>
<td>Park</td>
<td>Peter</td>
<td>54</td>
<td>R</td>
</tr>
<tr>
<td>Patel</td>
<td>Krupa</td>
<td>32</td>
<td>R</td>
</tr>
<tr>
<td>Pinkhasova</td>
<td>Diana</td>
<td>55</td>
<td>R</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polavarapu</td>
<td>Blood Sugar Control at Discharge And Its Association with Hospital Readmissions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rajagopal</td>
<td>Attitudes towards tissue donation for rapid autopsy among community and academic oncologists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robertson</td>
<td>HIV Infection Is an Independent Risk Factor for Decreased Six Minute Walk Test Distance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shoff</td>
<td>IL-6 and CRP Levels are Directly Associated with Monocytic-Myeloid Derived Suppressor Cell Frequencies in HIV(+) Individuals on ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smith</td>
<td>Physician clinical perspective of notifiable diseases (ND) and epidemiological data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thant</td>
<td>Overcoming barriers to Hepatitis C treatment in HIV/HCV coinfected patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umakanthan</td>
<td>Low Dietary Fiber Intake in Inflammatory Bowel Disease is Associated With Active Disease and Poor Quality of Life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varano</td>
<td>The Evaluation of the Reduction of Nitrite to Nitric Oxide via Carbonic Anhydrase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waheed</td>
<td>The Differential Effects of Gender on Mood symptoms, Health-related Quality of Life, Social Support, and Disease Severity Among Patients with Systolic Heart Failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waheed</td>
<td>Letters-to-the-Editor: A Novel Scholarly Activity in Residency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolfe</td>
<td>Pulmonary Vascular Resistance Predicts Mortality in End-Stage Renal Disease Patients with Pulmonary Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zupa</td>
<td>Does depression affect glycemic control and delivery of guideline-recommended care in patients with heart failure and diabetes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mechanisms of spontaneous fosfomycin resistance observed upon susceptibility testing of Escherichia coli

Presenter: Aaron Lucas, Resident Medicine
Research Interest: Bench Medicine

Mentors: Yohei Doi, MD, PhD
Funding Source: None

Authors: Aaron Lucas MD, Yohei Doi MD, PhD, Ryota Ito MD, PhD, Christi McElheny MS, Mustapha Mustapha MBBS, PhD, Anthony Pasculle ScD, Vaughn Cooper PhD

Introduction: Escherichia coli, the most common cause of urinary tract infections, has become increasingly resistant to commonly used oral antibiotics. This has led to the increased use of fosfomycin, a broad-spectrum cell wall synthesis inhibitor. However, the growth of E. coli “inner colonies” within the zone of inhibition around the fosfomycin disk, likely representing spontaneous mutants, complicates interpretation of susceptibility reporting. The goal of this study was to elucidate the fosfomycin resistance mechanisms of these inner colonies among ESBL-producing E. coli clinical strains.

Methods: Disk diffusion testing of fosfomycin (containing 200 ug fosfomycin, 50 ug of glucose-6-phosphate/disk) was performed on 496 ESBL-producing E. coli clinical isolates collected at UPMC between 2011 and 2015. For E. coli isolates producing inner colonies within or approaching the zone of inhibition defining resistance (≥12 mm in diameter), disk diffusion testing was repeated on the inner colonies to confirm that stable resistance had developed. Both the parental strains and their corresponding inner colony mutants were subjected to MIC testing and whole genome sequencing by NextSeq to identified SNPs.

Results: Of the 496 ESBL-producing E. coli strains, 21 produced inner colonies, and 6 produced colonies within or approaching the resistant zone of inhibition (≥12mm in diameter). MIC testing in 2 of the 6 pairs of parental strains and daughter inner colonies revealed greater MICs of the inner colonies versus the parents. The remaining 4 strains had inner colony MICs equal to the already non-susceptible parent. Whole genome sequencing revealed putative functional loss of uhpt, encoding the hexose-6-phosphate transporter, in all 6 inner colonies accounting for resistance or decreased susceptibility to fosfomycin, whereas other genes known to be involved in fosfomycin resistance, including glpT, murA, ptsI, and cyaA, were intact.

Conclusion: Among ESBL-producing E. coli strains at UPMC, 1.2% produced inner colonies upon fosfomycin disk diffusion testing, which would be interpreted as resistant in clinical microbiology laboratories. The mutants contained defective uhpt which accounted for the resistance. Fosfomycin-resistant mutants with loss of hexose-6-phosphate transporter have been shown to have decreased growth rates and fitness, but whether the occurrence of these mutants lead to treatment failure is uncertain. Further studies exploring these spontaneous mutants will provide valuable information to allow accurate reporting of fosfomycin susceptibility results.
**2-R Poster:** IL-6 and CRP Levels are Directly Associated with Monocytic-Myeloid DerivedSuppressor Cell Frequencies in HIV(+) Individuals on ART

**Presenter:** Christopher Shoff, Resident Medicine

**Research Interest:** Bench Medicine

**Mentors:** Bernard Macatangay MD

**Funding Source:** None

**Authors:** Christopher Shoff MD, Cynthia Klamar-Blain MSc, Arcadio Agudelo Hernandez MD, Yue Chen PhD, Charles Rinaldo PhD, Bernard Macatangay MD

**Introduction:** The role of myeloid derived suppressor cells (MDSC) in chronic inflammation and immune activation during treated HIV-1 infection has not been fully defined.

**Methods:** Peripheral blood mononuclear cells (PBMCs) and plasma were obtained from HIV-1(+), CMV antibody(+), participants who are virally suppressed on ART and with CD4+ T cell count >500, along with age-matched, CMV antibody(+), HIV-1-seronegative controls (SNCs) from the Multicenter AIDS Cohort Study. At three time points, frequencies of classical (Lin-CD33+HLA-DR-; cMDSC) and monocytic MDSCs (CD14+CD11b+CD33+HLA-DR-; mMDSC) as well as frequencies of patrolling (CD14dimCD16+) and inflammatory (CD14++CD16+) monocytes in live cells were evaluated using flow cytometry, while levels of sCD14, sCD163, IP-10, IL-6, D-dimer and CRP were measured in plasma using ELISA.

**Results:** Fifteen HIV(+) and twelve SNCs were enrolled in the study. HIV(+) participants had a median CD4+ T cell count of 803 cells/mm3 (range 555-1355). They had been infected for a median of 9 years and have been virally suppressed for a median of 6 years during the time of enrollment. There were no differences in the frequencies of mMDSCs (p=0.89; Mann-Whitney) and cMDSC (p=0.92) between HIV(+) and SNCs. Frequencies also remained stable across the three timepoints. Although there was an inverse relationship between %patrolling monocytes and %mMDSC in SNCs (r=-0.48; p=0.01; Spearman), this was not observed in HIV(+). Levels of IP-10 (p=0.002) and sCD14 (p<0.001) levels were significantly higher in HIV(+) participants across time points, but did not correlate with cMDSC and mMDSC frequencies. However, in SNCs, a modest negative correlation was seen between IP-10 levels and %mMDSC (r=-0.39; p=0.035). Levels of CRP, IL-6, and sCD163 were similar between the two groups and no correlations were seen between these biomarkers and %cMDSC and %mMDSC in SNCs. However, in HIV(+) participants, plasma levels of IL-6 and CRP directly correlated with %mMDSC (r=0.43; p=0.004 and r =0.40; p=0.011, respectively).

**Conclusion:** Increases in levels of systemic inflammation markers IL-6 and CRP correlate with higher frequencies of mMDSC in treated, chronic HIV infection, indicating the importance of immunoregulatory mechanisms in HIV.
**3-R Poster:** The Evaluation of the Reduction of Nitrite to Nitric Oxide via Carbonic Anhydrase

**Presenter:** Paul Varano, Resident Medicine

**Research Interest:** Bench Medicine

**Mentors:** Mark Gladwin MD

**Funding Source:** R01 (already present in lab)

**Authors:** Paul Varano MD

**Introduction:** Nitric Oxide is one of the most ubiquitous agents of endogenous vasodilatation in the biological world. The nitrite ion has been recognized as a biologically relevant source of nitric oxide. Carbonic Anhydrase II catalyzes the reaction between water and carbon dioxide to form carbonic acid. It has been that purposed carbonic anhydrase could catalyze reduction of nitrite into nitric oxide. Previous studies have shown this to be the case, and paradoxically have also demonstrated that acetazolamide - a known inhibitor of carbonic anhydrase - increases the reaction rate. Our lab sought to confirm these results or provide an alternative explanation for them.

**Methods:** Production of Nitric Oxide by Carbonic anhydrase Reactions were carried out in a Purge vessel attached to a General Electric Nitric Oxide Analyzer using helium as a carrier gas. Varying concentrations of sodium nitrite were mixed with lyophilized carbonic anhydrase II purified from bovine red blood cells purchased from Sigma Aldrich at pH 7.4 and 6.5. The enzyme was then tested with inhibitors Sulfanilamide, Acetazolamide, and bicarbonate. Two stocks of enzyme were used. One stock was purchased in 2008 and is of similar stock to that which was used in the original study. A second stock was purchased in 2016 also from Sigma Aldrich. To test for purity of the stock each sample was run on a SDS-PAGE gel.

**Results:** We found that the stock of Carbonic Anhydrase II from 2008 was able to catalyze the nitrite to nitric oxide reaction at pH 6.5 and 7.4. The carbonic anhydrase stock purchased in 2016 was only able to catalyze the reaction at pH 6.5. Interestingly, we did find that when inhibitor was present, it was possible to increase the rate of the reaction compared to without inhibitor present. SDS PAGE analysis was run to compare the purities of both stocks of carbonic anhydrase. We did find that the stock from 2008 was contaminated with Cu-Zn Superoxide dismutase, which was not present in the 2016 stock.

**Conclusion:** Although contamination with Superoxide dismutase may have augmented the results of the original study, it is possible that at low pH Carbonic anhydrase can catalyze the production of nitric oxide. However, given the that the reaction occurred at a far sub-physiologic pH, it is unlikely to be biologically relevant.
**Poster Abstracts**

**4-R Poster:** Provider interest in lifestyle tracking within the EHR: data from the MAINTAIN-pc study

**Presenter:** Jonathan Arnold, Resident Medicine  
**Research Interest:** Clinical

**Mentors:** Molly Conroy MD  
**Funding Source:** AHRQ

**Authors:** Jonathan Arnold MD, Dana Tudorascu PhD, Kathleen McTigue MD, Cindy Bryce PhD, Kimberly Huber MPH, Laurey Simkin-Silverman PhD, Rachel Hess MD, Gary Fischer MD, Molly Conroy MD

**Introduction:** Primary care providers (PCPs) can play a critical role in supporting patients’ ongoing weight maintenance. PCPs lack time and resources to support patients, many of whom use wearable devices and/or smartphone apps to monitor their progress toward lifestyle goals. There is increasing capability to integrate patient collected lifestyle data into the electronic health record (EHR), but less understanding of PCP interest in and potential use of these data.

**Methods:** Maintaining Activity and Nutrition through Technology-Assisted Innovation in Primary Care (MAINTAIN-pc) is an RCT of an EHR-based intervention for weight loss maintenance. We solicited feedback from participating PCPs via an anonymous web-based survey asking about their use of and interest in the study tools and their interest in other patient lifestyle data sources. Survey links were emailed in December 2016, after all subjects had completed at least 21 study months. Survey respondents were not paid but could choose to enter a prize drawing.

**Results:** To date we have received 18 responses to 65 surveys sent (28% response rate) across 6 different outpatient medicine practices. Respondents are 59% female and 94% white. Most (93%) have completed training over 10 years prior. 50% are full time clinicians, 44% clinician educators, and 6% clinician researchers. 72% of respondents “agree” or “strongly agree” that they are satisfied with MAINTAIN-pc. Most express interest in continuing to use the EHR-based tools with patients in MAINTAIN-pc after the study has completed (61% “yes,” 33% “maybe”) and will consider using them with new patients (11% “yes,” 67% “maybe”). Most PCPs are interested in the EHR integration of patient-collected lifestyle data from other devices and/or apps (50% “yes,” 33% “maybe”), specifically for physical activity (83%), weight (67%), and nutrition (61%). PCPs prefer to view summary reports of these data (56%) rather than reviewing all patient-collected data personally (22%) or by ancillary staff (6%). Most want to review reports on demand, prior to or during patient appointments (78%).

**Conclusion:** PCPs are largely satisfied with the MAINTAIN-pc EHR-based weight management intervention and tools. They are interested in integrating patient-collected lifestyle data into the EHR and prefer to review summary reports around the time of patient appointments, which is likely less time consuming than raw data review. This survey provides insight into how PCPs with experience using EHR-based tools for lifestyle management value the experience and their interest in future developments to support their patients’ lifestyle efforts.
5-R Poster: Effect of influenza vaccination in the severity of illness in hospitalized transplant recipients with laboratory-confirmed influenza

Presenter: Amy Bagenski, Resident Research Interest: Clinical Medicine

Mentors: Fernanda Silveira MD Funding Source: None

Authors: Amy Bagenski MD, Fernanda Silveira MD

Introduction: The effectiveness of influenza vaccine in solid organ transplant (SOT) recipients may be decreased due to immunosuppression. Some studies have suggested that influenza vaccination may decrease severity of illness in patients who become infected. The purpose of this study was to evaluate if influenza vaccination was associated with reduction in disease severity in SOT recipients hospitalized with influenza.

Methods: Adult SOT recipients hospitalized at a tertiary care medical center between 2009 and 2015 and with laboratory-confirmed influenza were enrolled. Data was prospectively collected and vaccination status was confirmed by review of electronic medical records.

Results: 51 SOT recipients hospitalized with laboratory-confirmed influenza were enrolled. 33 (64.7%) patients received influenza vaccine within the same season as infection. Ages ranged 27-79, with lung (n=24), renal (n=6), liver (n=8), heart (n=7), kidney and pancreas (n=5), and liver and pancreas (n=1) transplants. All patients received antiviral therapy. There was no significant difference in ICU requirement (9.1% vs. 16.7%, p=0.66), occurrence of superimposed pneumonia (45.4% vs. 50%, p=0.79), median length of stay (6 days vs. 5.5 days, p=0.68), discharge to home vs. extended care (87.9% vs. 88.9%, p=0.681), hospital mortality (6% vs. 0, p=0.53) or readmission (51.7% vs. 52.9%, p=0.77), when vaccinated SOT recipients were compared to unvaccinated. Superimposed pneumonia was more common in lung transplant recipients as compared to other SOT recipients; however, there was no difference in superimposed pneumonia for vaccinated vs. unvaccinated lung transplant recipients (37.5% vs. 29.2%, p=1.0).

Conclusion: Severity of illness in hospitalized SOT recipients with lab-confirmed influenza did not differ based on vaccination status within the same season. A larger sample size is needed to evaluate this further.
**Introduction:** Every year, influenza and pneumococcal infections contribute to severe illness and significantly increase hospitalizations. Vaccination rates for these infections have been noted to be sub-optimal; however, our study has shown that with the use of effective reminders in practice, the rates of vaccination against these illnesses can be improved upon.

**Methods:** We conducted a prospective observational study in adults 65 years of age or older. There was a pre-intervention phase which acted as a control, and a post-intervention phase which served as comparison. Interventions included electronic emailed daily reminders or staff-driven personal reminders to the residents directly. Inclusion criteria consisted of any patient who had been seen in our clinic and was age 65 years or older. Exclusion criteria for one or all of the vaccinations included documented refusal in the medical record, or ineligibility for a pneumococcal vaccine due to instructed dosing intervals. Data was obtained to a total sample size of 200 visit encounters. Pre-intervention dates ranged from December 15, 2015 through January 22, 2016. The intervention period began on January 25, 2016 and ran through February 17, 2016. These dates were chosen to incorporate flu vaccination season. The study data was obtained from our Electronic Health Record (EHR). Variables included patient’s gender and age, resident physician’s firm and level of training, and presence of egg allergy. We used Chi-squared and Fisher exact tests for statistical calculations to generate p-values for comparisons.

**Results:** The rate of influenza vaccination improved from 62.63% to 78.49% in the intervention group (P=0.016). Improvement was mainly noted in the personally-reminded case group (P=0.023). There was improvement in both PCV13 and PPSV23 vaccination rates from 67.78% to 78.65% in PCV13 and from 78.75% to 88.89% in PPSV23 groups. These improvements failed to reach statistical significance likely due to our study being underpowered. In the patient gender subsets, significant values were found for improvement in the rates of PCV13 vaccination in males (P=0.037) and flu vaccination in female patients (P=0.021). In the resident physician training year subsets, third year residents were the only group to show statistically significant improvement in flu vaccination (P=0.013).

**Conclusion:** Vaccination rates showed a trend of improvement after implementation of a reminder system. Overall, vaccination rates can be improved with appropriate attention to preventative care guidelines, teaching efforts, and a collaborative effort by all staff in the healthcare setting.
Poster Abstracts

7-R Poster: Trajectory of Physical Performance Measured by Gait Speed Indicates Risk for Adverse Outcomes in Liver Transplant Candidates

Presenter: Hui-Wei Chen, Resident Medicine
Research Interest: Clinical Medicine
Mentors: Michael Dunn MD
Funding Source: None
Authors: Hui-Wei Chen MD, Deborah Josbeno PhD, Amy Schmotzer RN, Amit Tevar MD, Doug Landsittel PhD, Michael Dunn MD

Introduction: Frailty measured by impaired physical performance is a potentially lethal consequence of cirrhotic muscle wasting, which can be anatomically measured on imaging as sarcopenia. Both frailty and sarcopenia measurements are known risk indicators for waitlist mortality and other adverse outcomes in liver transplant (LT) candidates. Whether the risk changes or is modifiable over time is not well known. We hypothesized that the rate of change in physical performance over time in LT candidates would reflect their risk of adverse outcomes.

Methods: We performed a prospective observational study of outcomes in 262 LT candidates who had physical performance tested by gait speed (m/sec) at 2 waitlist clinic visits separated by 30 days or more. We expressed their change in gait speed, dGS/dt, between the 2 visits as (m/sec)/month. We studied the association of dGS/dt with the subsequent adverse outcomes of waitlist deaths or removals for clinical deterioration, and hospital days for cirrhosis complications per 100 days at risk after the second visit. We assessed associations of dGS/dt with adverse outcomes by quartiles using the Poisson distribution.

Results: Our data shows the adverse outcomes of waitlist deaths or removals and hospital days/100 days associated with dGS/dt by quartiles over a mean 120 day observation period. dGS/dt in Quartile 1, 2, 3 and 4 were -0.059, 0.008, 0.004 and 0.060, respectively. Waitlist death or removal of each Quartile in order were 40.3%, 20.8%, 15.6% and 23.4%, respectively. Lastly, Hospital days at risk for each Quartiles were 4.84, 2.67, 2.44, and 2.71, respectively. Quartile 1, with the greatest negative dGS/dt, was associated with the highest occurrence of waitlist deaths or removals, 40.3% (P=0.002) and with the most hospital days, 4.84/100 days at risk (P=0.025), compared with the other 3 quartiles, which all showed non-significant variation in these outcomes.

Conclusion: Physical performance tested at a single time point has been associated with adverse LT waitlist outcomes. Our data show similar associations for dynamic change in a potentially modifiable performance measurement which may have value as a therapeutic target. Rapid functional performance decline identifies an especially high risk subset of LT candidates.
8-R Poster: Patterns between Multi-Year Steroid Use in Patients with Inflammatory Bowel Disease and Quality of Life, Disease Severity, Healthcare Utilization

Presenter: Debbie Cheng, Resident Medicine

Research Interest: Clinical Medicine

Mentors: David Binion MD

Funding Source: None

Authors: Debbie Cheng MD, Alyce Anderson BS, Claudia Ramos-Rivers MD, Benjamin Click MD, Ioannis Koutroubakis MD, Jana Hashash MD, Michael Dunn MD, Marc Schwartz MD, Jason Swoger MD, Arthur Barrie MD, Miguel Regueiro MD, David Binion MD

Introduction: Quality improvement measures for Inflammatory Bowel Disease (IBD) providers emphasize limiting steroid use, as prolonged use is associated with complications including infection, osteoporosis. The aim of this study was to characterize patterns of steroid use in IBD patients over multi-year time periods and the relationship with quality of life (QOL), healthcare use, and disease severity.

Methods: Patients followed in a prospective IBD natural history registry for >4 years from 2009 to 2015 were grouped based on low (<1 year), medium (2 to 3 years), and high steroid use (>4 years). Measures of disease activity, including Harvey-Bradshaw Index (HBI), Ulcerative Colitis Activity Index (UCAI); QOL using the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (with scores <50 indicating poor QOL); healthcare use, including total charges, ER and clinic visits, hospital admissions; narcotic use; antidepressant use were organized. Steroid usage groups were compared using ANOVA analysis for parametric measures and Kruskal-Wallis H for non-parametric ones.

Results: 1,457 patients were followed (47.0+15.5 years old, 52.4% female, 56.6% with Crohn's Disease, 34.8% with Ulcerative Colitis) and divided into low (63.7%, n=928), medium (24.3%, n=354), and high steroid use (12.0%, n=175) without a difference in age (p=0.44), disease type (p=0.094), mean BMI (p=0.25). Mean SIBDQ scores varied amongst groups (54.4+10.8 for low, 50.4+11.3 for medium, 48.6+10.9 for high use, p<0.001). The groups also varied in narcotic and antidepressant use, chronic abdominal ratings, as well as feeling discouraged, unable to conduct regular activities (all p<0.001). Steroid use also correlated with Clostridium difficile infection and vancomycin exposure (all p<0.001). Disease activity indices (UCAI, HBI) and healthcare utilization, including total charges, ER and clinic visits, and hospital admissions were found different amongst the groups (all p<0.001).

Conclusion: Most IBD patients require low steroid utilization, but a subset requires prolonged use given more severe and refractory disease. Quality measures for steroid use need to account for the difference amongst patients when assessing IBD providers. Steroid use also correlates with potentially modifiable measures, including worse QOL measures and increased use of narcotics and anti-depressants. By implementing multi-faceted care that focuses on pain management and psychiatric care, IBD providers may be able to improve steroid use amongst their patients.
10-R Poster: What is the Expected Incidence of Interval Colorectal Cancer (CRC) for an Endoscopist in Active Clinical

Presenter: Furkan Ertem, Resident Medicine
Research Interest: Clinical Medicine
Mentors: Robert Schoen MD, MPH
Funding Source: NCI
Authors: Furkan Ertem MD, Ateev Mehrotra MD, Rebecca Gourevitch MS, Uri Ladabaum MD, Robert Schoen MD, MPH

Introduction: Interval CRCs (I-CRCs), or CRCs detected after testing but before the date of the next recommended exam, are a concern for endoscopists. I-CRCs account for approximately 5% of CRCs. A higher adenoma detection rate (ADR) is inversely associated with subsequent I-CRC. Our aim was to estimate the number of I-CRCs an endoscopist might experience, and to consider the implications for quality assurance in colonoscopy.

Methods: We used 2 approaches to estimate I-CRCs per endoscopist: 1) a bottom-up approach starting with practice level data from UPMC health system; 2) a top-down approach starting with US national-level data. For both methods, we assumed that 5% of all CRCs were I-CRCs, and that the relative risk of I-CRC for endoscopists in the highest vs. lowest ADR quintile was 0.5, based on published studies. METHOD1: Using natural language processing, we analyzed colonoscopy reports in 14 hospitals in western Pennsylvania in the UPMC health system from 2013-15. We assessed the rate of CRC at colonoscopy, restricting the analysis to endoscopists performing >50 exams per year. METHOD2: We used 2016 SEER statistics, data on the number of US gastroenterologists, and data on the fraction of US colonoscopies performed by gastroenterologists for calculation.

Results: METHOD1: 91 endoscopists performed an average of 698 (range 100-2654) colonoscopies of which 317 (range 11-1552) were for screening over 2 years. There were 655 CRCs among 63,503 colonoscopies (approximately 1 CRC/100 colonoscopies). We estimated that an endoscopist performing 500 colonoscopies/year would therefore diagnose approximately 5 CRCs per year. If 5% of these were I-CRCs, then that endoscopist would experience approximately 1 I-CRC every 4 years, or 7-8 I-CRCs over a 30-year career. For the top vs. bottom ADR quintiles, the respective values would be approximately 1 I-CRC every 6 vs. 3 years.METHOD2: Given the US annual CRC incidence of 135,000, assuming 13,000 active US gastroenterologists, and estimating that gastroenterologists perform 75% of US colonoscopies, we calculated that an endoscopist would experience approximately 1 I-CRC every 2.6 years, or 12 I-CRCs over a 30-year career. For the top vs. bottom ADR quintiles, the respective values would be 1 I-CRC approximately every 4 vs. 2 years.

Conclusion: An endoscopist in active practice in the highest quintile of ADR can expect an I-CRC every 4-6 years vs. every 2-3 years in the lowest quintile. Thus, even the "best" endoscopists should expect I-CRCs. The low rate per endoscopist, the time delay to the event, and the complexity in ensuring accurate feedback to the endoscopist pose challenges to using I-CRC as a quality measure at the individual level. Intermediate or surrogate measures such as ADR may be the only viable alternative for measuring quality in practice.
**Poster Abstracts**

**11-R Poster:** Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experiences (APPRENTICE): An International Multicenter Consortium for the study of Acute Pancreatitis

**Presenter:** Amir Gougol, Resident  
**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Mentors:** Georgios Papachristou MD, PhD  
**Funding Source:** None

**Authors:** Amir Gougol MD, Mohannad Dugum MD, Jorge Machicado MD, Carl Manzo MD, Georgios Papachristou MD, PhD

**Introduction:** APPRENTICE is an international multicenter consortium that was developed in July 2014 as an initiative supported by the Collaborative Alliance for Pancreatic Education and Research (CAPER). Aim: To better understand the natural history of acute pancreatitis (AP), assess differences in management worldwide, and develop a platform for future randomized clinical trials.

**Methods:** After initial meetings of representatives from a number of United States and international medical centers with established expertise in pancreatic diseases, institutional review board approval for the study was obtained from all included centers. Detailed web-based questionnaires were then developed to prospectively record data on demographics, comorbidities, risk factors, etiology, clinical course, markers of severity, healthcare utilization, management strategies, and clinical outcomes of AP. Study data are collected and managed using REDCap (Research Electronic Data Capture) tools hosted at each center. All data entered into the REDCap database is systematically reviewed by the coordinating center (University of Pittsburgh). Patient enrollment started in November 2015 and is ongoing.

**Results:** Between November 2015 and September 2016, a total of 509 patients have been prospectively enrolled into APPRENTICE from 20 medical centers (8 in the United States, 5 in Europe, 3 in South America, 2 in Mexico and 2 in India). Interim data analysis showed: mean age of patients is 51 years (SD is 19), 49% are male, 47% are white, and 33% are Hispanic. The leading cause of AP is biliary (46%), followed by idiopathic (17%), alcohol (14%), post-ERCP (12%), then hypertriglyceridemia (5%). About one quarter of the patients had recurrent AP.

**Conclusion:** APPRENTICE is an international collaboration of tertiary AP centers that has demonstrated feasibility in forming a large, prospective, multicenter patient registry to study AP. Analysis of collected data will provide greater understanding of AP. APPRENTICE will serve as a future platform for randomized clinical trials to assess new therapies in a diverse patient population.
12-R Poster: Association of Dietary Habits with Severe Acute Pancreatitis

Presenter: Amir Gougol, Resident
Gastroenterology, Hepatology and Nutrition

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Georgios Papachristou MD, PhD

Funding Source: None

Authors: Amir Gougol MD, Mohannad Dugum MD, Carl Manzo MD, Jorge Machicado MD, Adam Slivka MD, David Whitcomb MD, PhD, Dhiraj Yadav MD, Georgios Papachristou MD, PhD

Introduction: The revised Atlanta classification stratifies acute pancreatitis (AP) based on the development of local complications and/or organ failure into mild, moderate, and severe disease. The relation between diet and risk of AP has been suggested by prior studies, but the association of dietary habits with AP severity has not been previously evaluated. Aim: Assess differences in severity of AP based on reported dietary habits.

Methods: A prospectively maintained cohort of patients with AP admitted to a tertiary medical center between 2008 and 2015 was utilized. A questionnaire with details on dietary habits was completed by interviewing enrolled subjects during their hospitalization. Patients were stratified into two groups: mild/moderate AP and severe AP. Dietary habits were categorized based on the overall type of diet, fruits/vegetables servings, fat content, dairy consumption, and fluid intake. Multivariate analysis was used to determine whether dietary habits have an independent association with severity of AP. P-value = 0.05 was considered statistically significant.

Results: A total of 309 prospectively enrolled patients had available dietary habits questionnaires: 153 (49.5%) male, mean age was 51 years. Two hundred and forty (77.7%) developed mild/moderate AP and 69 (22.3%) developed severe AP. No differences in etiology of AP were present between both groups. Patients who developed severe AP were more likely to consume < 3 servings of fruits/vegetables per day (81% versus 60%, p=0.003) prior to the onset of AP, had a lower mean daily fluid intake (47.1 Oz versus 55.8 Oz, p=0.05), and a lower ratio of fluid intake to BMI (1.5 versus 1.9, p=0.03). No differences in the diet fat content (p=0.59), or dairy consumption (p=0.55) were present between both groups. Multivariate analysis controlling for gender, age, etiology of AP, smoking, and alcohol intake, showed an independent association between fruit/vegetables intake (odds ratio: 0.35) and ratio of fluid intake to BMI (odds ratio: 0.5) with the development of severe AP.

Conclusion: A diet poor in fruits and vegetables and decreased fluid intake are independently associated with severe disease in patients with AP. These important findings require further evaluation and may be useful in patient counseling and risk stratification.
**13-R Poster:** Clinical Outcomes of Isolated Renal Failure Compared to Other Forms of Organ Failure in Patients with Severe Acute Pancreatitis

**Presenter:** Amir Gougol, Resident  
Gastroenterology, Hepatology and Nutrition

**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Mentors:** Georgios Papachristou MD,PhD  
Funding Source: None

**Authors:** Amir Gougol, MD

**Introduction:** According to the revised Atlanta classification, severe acute pancreatitis (SAP) is characterized by persistent organ failure (OF) lasting more than 48 hours. Persistent OF includes isolated OF or multiple OF. The specific clinical outcomes of SAP complicated by isolated renal failure (RF) are not well characterized. We aimed to assess differences in clinical outcomes of SAP complicated by isolated RF compared to other forms of OF.

**Methods:** Using a prospectively maintained database of patients with acute pancreatitis admitted to a tertiary medical center between 2003 and 2016, those with evidence of persistent OF were identified: renal, pulmonary, cardiovascular, or multi-organ (2 or more organs). Data regarding demographics, comorbidities, etiology of SAP, and clinical outcomes were prospectively recorded. Differences in clinical outcomes after development of isolated RF in comparison to other forms of OF were determined using independent t and Mann-Whitney U tests for continues variables, and chi-square test for discrete variables.

**Results:** Among 500 patients with acute pancreatitis, 111 patients developed persistent OF: mean age was 54.2 years, and 75 (67.6%) were male. Forty-three patients had isolated OF: 17 (15.3%) RF, 25 (21.6%) pulmonary failure (PF), and 1 (0.9%) patient had cardiovascular failure. No differences in demographics, etiology of SAP, systemic inflammatory response syndrome scores, or development of pancreatic necrosis were present between isolated RF and PF. Patients with isolated RF were less likely to require nutritional support (NS) (76.5% vs. 96%, p=0.001), ICU admission (58.8% vs. 100%, p=0.001), and had shorter mean ICU stay (2.4 vs. 15.7 days, p<0.001), compared to isolated PF. None of the patients with isolated RF or PF died.

**Conclusion:** Among patients with SAP per the revised Atlanta classification, approximately 15% develop isolated RF. This subgroup has a less protracted clinical course compared to other forms of OF. Isolated RF should be weighed less than isolated PF in risk predictive modeling.
**14-R Poster:** Different demographic, clinical and severity profile between patients with recurrent and first attack of acute pancreatitis (AP)

**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Funding Source:** None

**Authors:** Jorge Machicado MD, Amir Gougol MD, Mohannad Dugum MD, Carl Manzo MD, Gong Tang PhD, Adam Slivka MD, David Whitcomb MD, PhD, Dhiraj Yadav MD, Georgios Papachristou MD, PhD

**Introduction:** Few studies have studied the differences between a first attack of AP and subsequent attacks of recurrent acute pancreatitis (RAP). Our aim was to compare the demographic factors, clinical profile, and outcomes between patients with a first and recurrent AP attack.

**Methods:** We used data from a single-center prospective cohort that has enrolled well-phenotyped AP patients at the University of Pittsburgh Medical Center between 2004-2015. RAP was defined as at least two documented episodes of AP with more than three months in between attacks. Patients with chronic pancreatitis were excluded. Data on demographics, comorbidities by Charlson Comorbidity Index (CCI), etiology, severity by Revised Atlanta Classification, interventions, multisystem organ failure, pancreatic interventions, prolonged length of stay (LOS, > 7 days), and mortality was obtained. To determine the independent effect of a RAP attack, odds ratio (OR) was calculated with binomial logistic regression for binary outcomes and relative risk (RR) with multinomial logistic regression for outcomes with more than 2 categories (severity). Covariates such as age, gender, race, obesity, CCI, etiology, and transfer status were adjusted in these models.

**Results:** 145 (31%) patients had RAP, and 326 (69%) first AP attack. RAP patients were significantly younger (P<0.001), less obese (P<0.01), more likely to be smokers (P<0.001), and less likely have been transferred from another institution (P<0.001), than those with first-episode AP (Table 1). Alcoholic, hypertriglyceridemic, and idiopathic etiology occurred more likely in RAP vs. first AP attack (P<0.001). In logistic regression models, RAP attacks were associated with decreased odds of severe AP (RR 0.4, CI 0.2-0.9), multiorgan system failure (OR 0.4, CI 0.2-1) and prolonged hospital stay (OR 0.6, CI 0.4-1) than first AP attacks. No difference in the odds of moderately severe AP, need for pancreatic interventions or mortality was seen between AP patients with first or recurrent attacks.

**Conclusion:** RAP attacks tends to be less severe than first AP attacks. Furthermore, RAP patients have different demographic and clinical profile than those with first attack of AP. More studies are needed to better characterize the clinical profile and natural history of RAP.
**15-R Poster:** Frequency and clinical predictors of pain and disability after 1 year of AP: A single center prospective study

**Presenter:** Amir Gougol, Resident 
**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Mentors:** Georgios Papachristou MD, PhD 
**Funding Source:** None

**Authors:** Jorge Machicado MD, Amir Gougol MD, Mohannad Dugum MD, Carl Manzo MD, Adam Slivka MD, David Whitcomb MD, PhD, Dhiraj Yadav MD, Georgios Papachristou MD, PhD

**Introduction:** Little is known about the natural history and risk factors of pain and disability in survivors of acute pancreatitis (AP). The aim of this study was to assess the frequency and clinical predictors of pain and disability after 1 year of AP.

**Methods:** Consecutive patients prospectively enrolled between September 2011 and June 2015 at UPMC during first or recurrent AP attack, were followed-up approximately 1 year after enrollment (median: 14 months, IQR: 11-15). Baseline data including demographics, comorbidities, history of recurrent AP (RAP), etiology, severity by Revised Atlanta Classification (RAC), and outcomes, were prospectively obtained during hospitalization. Patients with chronic pancreatitis, or who died before follow-up were excluded. Eligible subjects (n=153) were approached through a telephone or regular mail survey that included items on pain, analgesic use, and disability. Presence in the last 4 weeks of pain that interfered with their normal work or abdominal pain subjectively attributed to pancreatitis (presence, pattern) was recorded. Logistic regression analysis was used to assess predictors of abdominal pain at follow-up, and final models included only factors with P<0.05. Given the small sample size of patients with disability, regression models were not performed in this group, and results of univariable analyses are presented.

**Results:** A total of 110 (72%) AP patients responded the survey. Median age was 51 years (IQR, 36-67), 42% were male, 95% were white, 64% had first attack, 47% had biliary etiology, and 14% had severe AP. During the 4-week period before follow-up, 41% had any type of pain that interfered with their work, 24% had abdominal pain (62% intermittent, 38% constant), and 10% used analgesics on a regular basis (63% opiates). Disability was reported by 8% of patients. Factors associated on logistic regression models with abdominal pain at follow-up included idiopathic etiology (OR: 3.8), history of RAP (OR: 2.9), and organ failure (OR: 3.3) (Table 1). Younger age (P<0.01), obesity (P<0.05), current smoking (P<0.05), alcoholic etiology (P<0.05), and pancreatic necrosis (P<0.05), were associated with abdominal pain at follow-up on univariable analysis but not in multivariate models. Disability at follow-up was associated with current smoking (P<0.001) and ICU admission (P<0.05) on univariable analysis. Comorbidities, severity by RAC and pancreatic interventions, were not associated with abdominal pain or disability at follow-up.

**Conclusion:** After one year of AP, pain is occasionally present and disability is usually absent. Idiopathic etiology, history of RAP, and organ failure are independent factors associated with abdominal pain at 1-year follow-up of AP. Future research is needed to understand the mechanisms of pain following AP recovery.
**16-R Poster:** Pre-existing diabetes is an independent risk factor of severity, pancreatic interventions, and length of stay in patients with acute pancreatitis

**Presenter:** Amir Gougol, Resident  
**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Mentors:** Georgios Papachristou MD, PhD  
**Funding Source:** None

**Authors:** Jorge Machicado MD, Amir Gougol MD, Mohannad Dugum MD, Carl Manzo MD, Gong Tang PhD, Adam Slivka MD, David Whitcomb MD, PhD, Dhiraj Yadav MD, Georgios Papachristou MD, PhD

**Introduction:** Diabetes mellitus is associated with increased risk of acute pancreatitis (AP). However, the effect of pre-existing diabetes on the clinical course of AP has not been well established. Therefore, our aim was to determine the effect of pre-existing diabetes in severity and outcomes of AP.

**Methods:** The Severity of Acute Pancreatitis/Pancreatitis-associated Risk of Organ Failure (SAPS/PROOF) is a prospective study at the University of Pittsburgh that has enrolled a large number of well-phenotyped AP patients between 2004-2015. A case-control design was used to compare demographics, comorbidities by Charlson Comorbidity Index (CCI), etiology, severity by Revised Atlanta Classification, pancreatic interventions (drainage, debridement), mortality, and prolonged length of stay (LOS, > 7 days), between AP patients with and without pre-existing diabetes. To determine the independent effect of pre-existing diabetes, odds ratio (OR) was calculated using binomial logistic regression for dichotomous outcomes and relative risk (RR) with multinomial logistic regression for outcomes with more than 2 categories (severity). Models were adjusted for other covariates such as age, gender, race, obesity, CCI, etiology, and prior attacks of AP.

**Results:** Out of 471 patients, 105 (22%) had pre-existing diabetes. Median age was 51 (IQR 36-67), 50% were female, 88% were white, 46% were obese, 69% had no prior AP attacks, and 41% had gallstone etiology. Compared with non-diabetics, those with diabetes had higher CCI (P<0.001) and were more likely to be older (P=0.02), black (P=0.01), and obese (P=0.001). Biliary (47 vs. 39%) and hypertrygliceridemic (25 vs. 4%) etiologies were more common in diabetics vs. non-diabetics (P<0.001). On logistic regression models, pre-existing diabetes was independently associated with larger odds of moderately AP (RR=2.2), severe AP (RR=2), pancreatic interventions (OR=2.1), and prolonged LOS (OR=1.7) than nondiabetics (Table 1). The odds of multisystem organ failure or mortality were not different between AP patients with and without pre-existent diabetes.

**Conclusion:** Pre-existing diabetes is an independent risk factor for moderately severe and severe AP, pancreatic interventions, and prolonged length of stay in AP patients. Larger multicenter studies are needed to validate our findings.
17-R Poster: Improvement in Ejection Fraction after Cryoballoon Pulmonary Vein Isolation for Atrial Fibrillation (AF) in Individuals with Systolic Heart Failure

Presenter: Emily Guhl, Resident Medicine

Research Interest: Clinical Medicine

Mentors: Sandeep Jain MD

Funding Source: None

Authors: Emily Guhl MD, Evan Adelstein MD, Raveen Bazaz MD, Jan Nemec MD, Andrew Voigt MD, Norman Wang MD, Samir Saba MD, Sandeep Jain MD

Introduction: Cryoballoon Pulmonary Vein Isolation (PVI) is a commonly used treatment modality for rhythm control of atrial fibrillation (AF). Patients with systolic dysfunction and AF may benefit from a strategy of rhythm control. Data are limited examining the outcomes of Cryoballoon PVI in patients with systolic heart failure (HF).

Methods: We evaluated a single-center prospective registry of patients undergoing Cryoballoon PVI between 8/2011 and 6/2016 to identify patients with evidence of systolic HF (EF<55%) between the time of AF diagnosis and their Cryoballoon PVI procedure. We collected baseline characteristics at the time of procedure as well as serial ejection fraction (EF) measurements. Patients were assessed for AF recurrence at 6 months and 1-year post procedure, with a 3-month blanking period. Recurrence was based on symptoms, ECG, or event monitor evidence of AF. Baseline characteristics, as well as EF recordings throughout, were compared between individuals with and without AF recurrence at 1-year.

Results: Final analysis included 56 patients with HF undergoing Cryoballoon PVI with a mean age 57.7±10.5 years, 52% hypertension, 5.4% female, CHA2DS2VASC 1.6±1.3, 65.5% persistent AF, EF at diagnosis 37±10%, and EF at time of procedure 44±10%. An AF diagnosis for =1 year prior to ablation was present in 61.8% and 53.7% had systolic HF for =1 year pre-procedure. The AF recurrence-free rate at 1-year for individuals with systolic HF was 50.9%. Of the patients who were AF recurrence-free at 1-year, 16.6% were still taking anti-arrhythmic drugs. There were no significant differences in baseline characteristics between individuals with recurrence of AF at 1-year vs. those without. For the patients that had echocardiograms performed at 1-year (n=39), a greater proportion of individuals without AF recurrence had an improvement in EF of = 10% than in those with AF recurrence (52.6% vs 20.0%, p=0.034).

Conclusion: In patients with systolic HF, Cryoballoon PVI provides an acceptable AF recurrence-free rate at 1-year of approximately 50%. Maintenance of sinus rhythm by Cryoballoon PVI was associated with improvement in ejection fraction. Further evaluation is needed to determine the potential role of early Cryoballoon PVI in patients with a new diagnosis of HF and AF.
Introduction: Cirrhosis secondary to Nonalcoholic Steatohepatitis (NASH) is projected to become the leading indication for liver transplantation (LT) in the United States in the next decade. The outcomes of patients undergoing LT for NASH, as well as the development of recurrent NASH have been well reported. The long-term implications however, of post LT NASH, specifically on the development of allograft cirrhosis are not well known.

Methods: A retrospective cohort of patients at a single large center undergoing LT for NASH from 2000-2015 were identified using a prospectively collected database. Demographic variables and outcomes were noted. The diagnosis of allograft cirrhosis was based on a combination of histology and clinical parameters.

Results: A total of 226 patients undergoing LT for NASH were identified. Mean follow up was: 7 years. 1, 5 and 10 year patient survival were 82, 73 and 62% respectively. 75% of patients underwent at least one biopsy post LT. Eighty-one patients (34%) developed evidence of recurrent NASH at mean follow up of 3 years. Fifteen patients developed at least bridging fibrosis as a result of recurrent disease with only four patients progressing to cirrhosis at a mean of nine years post LT. BMI at the time of transplant was statistically higher in those who developed recurrent NASH cirrhosis. The four patients with recurrent NASH cirrhosis all developed evidence of portal hypertension, but none have died and none have been re-listed for LT.

Conclusion: Although recurrent disease is relatively common in patients undergoing LT for NASH, the development of recurrent graft cirrhosis secondary to NASH at a mean of 7+ years follow up is rare.
Introduction: Infective endocarditis (IE) is a life threatening infection with mortality approaching 50% when complicated by heart failure and/or cerebrovascular accidents. With increasing prevalence in western Pennsylvania, surgery is potentially life saving and may be required in about 25 – 50% of cases. We sought to review epidemiologic trends and outcomes in patients treated with surgical intervention at our institution.

Methods: We performed a retrospective observational review of patients that underwent valve surgery at UPMC Mercy hospital in Pittsburgh, Pennsylvania. 232 patients that underwent valve surgery were screened over a 4 year period from 2011-2015. Data including basic demographics, diagnostic criteria, surgical complications, and outcomes were collected from patients that underwent surgery for treatment of endocarditis.

Results: Overall, 42 cases of endocarditis treated with valve surgery were analyzed; median age was 44.2 years, Left sided endocarditis accounted for 39 (92.8%) of patients: native valve IE in 36 (85.7%) patients. IV drug use was present in 24 (57.14%) of patients. Leading causative microbial pathogens included MSSA, 12 (28.6%) and Streptococcus spp in 12 (28.6%) patients. MRSA infection only accounted for 4 (9.5%) patients. Most common indication for surgery was heart failure 25 (59.5%). Preoperative intracranial septic emboli were present in 10 (23.8%) patients. Mean time to surgery was 8 days, with complications noted in 19 (45.2%) of patients. Post-operative renal replacement therapy 4 (9.5%) and permanent pacemaker implantation 4 (9.5%) were the most common complications. 4 (9.5%) patients died in the hospital while 9 (21.4%) patients were deceased at 1 year.

Conclusion: Valve surgery is considered optimal therapy in patients with complicated IE. Often the decision about whether surgical intervention is necessary and the optimal timing is complex. In our contemporary population based study, the average time to surgery was 8.1 days from admission. Multiple valve surgery was associated with a longer ICU length of stay. Although IVDU is classically associated with right sided IE, 75% of IV drug users had left-sided IE in our population. Patients with IE complicated by embolic phenomena (28.6%) were more likely to be readmitted within 90 days. Heart failure was the most common indication for surgical intervention, also showing a trend toward increased 1 year mortality.
**Introduction:** Multiple gestational births are a reported risk factor for peripartum cardiomyopathy (PPCM), but the impact on myocardial recovery in PPCM has not been studied. In addition, the effect of breastfeeding on maternal outcomes remains controversial. We investigated the effect of multiple births, breastfeeding, and method of delivery on myocardial recovery through analysis of the IPAC (Investigations in Pregnancy-Associated Cardiomyopathy) study.

**Methods:** 100 women with PPCM were enrolled at 30 centers within three months postpartum. Information regarding multiple versus singleton births, method of delivery, and breastfeeding were collected at time of entry. Women were followed for up to 12 months postpartum, and left ventricular ejection fraction (LVEF) was assessed by echocardiography at entry, 6 months and 12 months postpartum.

**Results:** Nineteen women (19%) of the IPAC cohort presented after giving birth to either twins (16%) or triplets (3%). When compared to IPAC women presenting after single pregnancies, women presenting after a multi-fetal birth had a better LVEF at entry (0.39 +0.07 vs 0.33+0.10, p=0.03), which persisted at 12 months postpartum (12 month LVEF 0.60+0.04 vs 0.51+0.11, p=0.004). For method of delivery, 50% of women in IPAC underwent C-section, and there was no significant difference in LVEF for women undergoing vaginal delivery versus C-section at entry (0.34+0.10, 0.35+0.10, p=0.50), 6 months (0.51+0.12, 0.52+0.09, p=0.82), or 12 months postpartum (0.52+0.11, 0.55+0.09, p=0.22). For women who breastfed (15%) there was a trend for a higher LVEF at entry (0.39+0.06, 0.34+0.10, p=0.06), which persisted at 6 months (0.56+0.05, 0.50+0.11, p=0.048) and 12 months postpartum (0.57+0.04, 0.52+0.11, p=0.10). There was no evidence that breastfeeding limited recovery.

**Conclusion:** Nearly 20% of women in IPAC presented after a multiple birth. While this remains a risk factor for the development of PPCM, it did not impact myocardial recovery. Similarly, method of delivery and breastfeeding did not appear to impact outcomes, and these decisions should focus on the immediate needs of the mother and child, as there is no clear impact on maternal myocardial recovery.
**21-R Poster:** cfDNA Mutation Frequency in Early Stage Breast Cancer

**Presenter:** Karthik Joshua Kota, Resident Medicine  
**Research Interest:** Clinical Medicine

**Mentors:** Steffi Oesterreich PhD, Adrian Lee PhD, Rekha Gyanchandani PhD  
**Funding Source:** Breast Cancer Research Foundation

**Authors:** Karthik Kota MD, Rekha Gyanchandani PhD, Margaret Rosenzweig PhD, Adam Brufsky MD, Shannon Puhalla MD, Lori Miller BS, Steffi Oesterreich PhD, Adrian Lee PhD

**Introduction:** Though 93% of patient present with early stage breast cancer (EBC), metastatic recurrence is expected in 7-13%. To prevent estrogen receptor (ER) positive disease recurrence, endocrine therapy (ET) is given after local disease. ET guidelines recently extended therapy — specifically tamoxifen—from 5 years to 10 based on ATLAS and aTTom. This pilot study used blood samples from women 6 months post-ET to determine cell free DNA (cfDNA) mutation prevalence in disease-free patients.

**Methods:** Patients with EBC and continued follow-up after ET were recruited from the Magee Women's Breast Cancer Clinic. Inclusion criteria were EBC, ER+, and completion of ET >6 months prior to visit; the exclusion criterion was active disease. Patients gave 2 blood samples, placed in Streck and EDTA tubes and processed at 2 laboratory sites for cfDNA. Blood from patients with metastatic breast cancer (MBC) served as controls for mutation detection. cfDNA was amplified for ESR1 and PIK3CA genes. Targeted amplifications underwent digital droplet PCR to identify mutations: 4 for ESR1 (D538G, Y537C/N/S), 2 for PIK3CA (E545K, H1047R)

**Results:** Ten EBC patients >6 months post-ET (post-EBC; 2/5/3 of stage I/II/III) and 10 MBC patients gave samples. cfDNA yield between plasma isolated from EDTA and Streck tubes (including mutation allele frequencies) was not significantly different (p >0.05); cfDNA yield from patients with MBC was >2X higher than post-EBC (p <0.001). MBC cfDNA had 2 monoclonal and 1 polyclonal (2 different) mutations in ESR1, while post-EBC cfDNA had none.

**Conclusion:** This pilot study shows cfDNA can be consistently isolated from Streck or EDTA-processed blood from patients with MBC and post-EBC; however, cfDNA levels are significantly higher in MBC. There were no mutations (ESR1 or PIK3CA) in post-EBC samples, though ESR1 mutations were found in MBC. Further studies are needed to determine if mutations in cfDNA can be found in patients without evidence of disease.
22-R Poster: Do Internal Medicine Residents Know How to Deprescribe?

Presenter: Karthik Joshua Kota, Resident Medicine
Research Interest: Clinical

Mentors: Rollin Wright MD, Steven Handler MD, Jennifer Pruskowski PharmD
Funding Source: Start-up funding (Geriatrics Division)

Authors: Karthik Kota MD, Jennifer Pruskowski PharmD, Rollin Wright MD, Steven Handler MD

Introduction: Physician trainees do not routinely deprescribe medications in older patients or those with life-limiting illnesses. Deprescribing—the process of stopping medications when harms outweigh benefits in a clinical context—is a skill teachable via structured processes. The goal of this study was to assess internal medicine (IM) residents’ attitudes and knowledge about deprescribing.

Methods: Over 3 months, UPMC Presbyterian IM residents completed an anonymous, online survey on deprescribing in older adults. Sections included demographics, attitudes, self-efficacy, and vignettes. Ten vignettes were presented to residents allowing them to deprescribe in situations ranging from remaining life expectancy to time-until-effectiveness, and asking them to rank barriers/concerns to deprescribing.

Results: The response rate was 48.5% (98/202), with about 36% post-graduate year (PGY)-1s, 33% PGY-2s, 28% PGY-3s, 2% PGY-4s, 2% PGY-5s; 96% had a primary care clinic. Regarding deprescribing, 33% felt unable to implement the practice; 39% felt they needed supervision; and 39% felt able to deprescribe alone. Nearly all (97%) agreed deprescribing should occur in a primary care provider (PCP) visit, while 81% agreed it could occur during non-PCP visits. About 70% thought PCPs could discontinue medications started by other providers if timely communication occurred, while 46% thought any physician, not just the PCP, had the right to do so. Nearly 60% were comfortable deprescribing a PPI or statin, while only 37% said the same for insulin. Most (80%) could not deprescribe in the last year because of several barriers, including clinical complexity (39%), incomplete information on past rationales/tolerance of medications (30%), and uncertainty of benefits and harms (37%). The top 3 barriers to deprescribing were knowledge-based uncertainties, not systems-based issues (e.g., time constraints) or patient attitudes.

Conclusion: This study shows IM residents have difficulty deprescribing in older adults and in certain clinical contexts. These data show the need for more concrete decision aides (like STOPP-START) to help IM residents deprescribe medications.
23-R Poster: Three Habits of Highly Effective Residents in Outpatient Clinic

Presenter: Karthik Joshua Kota, Resident Medicine
Research Interest: Clinical Medicine

Mentors: Gary Fischer MD, Amar Kohli MD
Funding Source: None
Authors: Karthik Kota MD, Amar Kohli MD, Gary Fischer MD

Introduction: Providing efficient care in outpatient practice is crucial for residents to master. Current research, however, focuses on office staff and flow, not physician efficiency. The few studies on residents and efficiency (none in Internal Medicine) focus on precepting before starting the day, documentation in forms, preparatory primary care "boot camps," and motion studies. To discover how residents become efficient, this study conducted one-on-one interviews to elicit trends and themes on efficiency and inefficiency.

Methods: Internal medicine residents with primary care clinic at the University of Pittsburgh Physicians - General Internal Medicine (Oakland) Clinic were invited (by email and study coordinators) to one-on-one, semi-structured interviews conducted by phone and recorded for later transcription. The semi-structured format included questions on practice style, office visit mechanics, 2 vignettes (1 urgent care, 1 complex primary patient), and thoughts on efficiency. Interviews were transcribed by one author and verified by another. Respondents' names were not included in transcriptions. Coding was done separately by two authors and compared prior to final analysis.

Results: 8 of 9 recorded interviews have been transcribed, with further interviews planned; averaging 25 minutes, interviews ranged from 13 to 37 minutes. Of those transcribed, 4 graduated (Post Graduate Year (PGY)-4), 2 were PGY-3, and 2 were PGY-2; 2 self-described as inefficient, 6 as efficient. Several themes emerged. Inefficient residents looked up patients prior to clinic; efficient ones did so the day of clinic. Inefficient residents did not write notes while in the room, while efficient ones (with one exception) at least started a note in the room (of note, nearly all efficient residents stressed starting notes early). Efficient residents lumped activities before precepting (e.g., pelvic exams, pending orders), while inefficient residents deferred activities until approved by attendings. Of note, no resident was ever asked to change their note.

Conclusion: Preliminary analysis shows clear differences between residents who self-identify as efficient and inefficient. Though of similar quality (as determined by the lack of needing to change or addend notes), self-identified efficient residents are more independent, spend less time preparing (e.g., pre-reading, planning notes as opposed to starting them), and are more focused (e.g., urgent care is for urgent care, not health maintenance). Initial efforts to improve resident efficiency may focus on encouraging independent action, focusing visits, and facilitating starting notes in the room (e.g., templated common outpatient presentations).
24-R Poster:  Clinical characteristics of inflammatory bowel disease (IBD) patients requiring long-term parenteral nutrition support in the present era of immunomodulator and biologic therapy

Presenter:  Michael Kurin, Resident Research Interest:  Clinical Medicine
Mentors:  David Binion MD
Authors:  Michael Kurin MD, Gina Kozak PA, Jana Al Hashash MD, David Levinthal MD, Elisabeth Kramer MD, Miguel Regueiro MD, Patricia Centa CNSC, Juliette Bender-Heine PA, Michael Dunn MD, Claudia Ramos Rivers PhD, David Binion MD

Introduction: Despite advances in the medical management of IBD, a subset of refractory patients require extensive surgery leading to short gut syndrome/intestinal failure requiring long-term total parenteral nutrition (TPN) or customized intravenous fluid (IVF) support. Our aim was to characterize the IBD patients requiring home TPN/IVF with a focus on treatment requirement, healthcare charges and clinical outcomes.

Methods: Observational study from a prospective IBD research registry from a tertiary facility from 1/1/2009 – 12/31/2015. Patients receiving long-term home TPN/IVF support (>2 months) were identified (TPN IBD) and were compared with remaining IBD patients (IBD). Demographics, surgical history, smoking history, narcotic use, IBD treatment history, and health care charges were reviewed. IBD specific treatment (period prevalence) included prednisone, mesalamine, immunomodulators anti-TNF biologic agents (infliximab, adalimumab, certolizumab) and anti-integrin biologics (natalizumab, vedolizumab). IBD TPN group was then divided into three groups based on median healthcare charges and same analysis performed.

Results: Out of 2359 IBD patients there were 1.1% (n=26) who required home TPN/IVF (TPN IBD) and the remaining 2333 formed the control population (IBD). There was no difference in age (TPN IBD 51.6±12.5y vs. IBD 46±15y; p= 0.06), or gender. Crohn’s disease was found in 58% of IBD group and 92.3% of TPN IBD (p<0.001). Median duration of TPN use was 29 months (quartiles 12-75.8). TPN was significantly associated with smoking, narcotic use, IBD-related surgeries and lower quality of life scores (SIBDQ). There were similar rates of immunomodulator and biologic use in TPN IBD and IBD cohorts (Table 1). Among TPN IBD, the growth factor teduglutide was used in 7 individuals, facilitating TPN discontinuation in 3 patients. An additional 4 IBD patients weaned off TPN/IVF for a total of 7/26 (26.9%) who were able to successfully discontinue this modality. Median healthcare charges in the TPN IBD were $42,000 annually while median charges in the IBD cohort were $3,400 (P<0.0001). Period prevalence mortality in TPN IBD was 11.5% and 3.8% in the IBD cohort (p=0.08). In subgroup analysis of TPN IBD, there is a trend towards more narcotic use, smoking, surgeries, lower mean SIBDQ scores in higher cost patients, meeting significance for surgeries only (Table 2).

Conclusion: IBD patients requiring long-term home TPN/IVF support are a small minority of a tertiary referral population (1.1%) in the present era of immunomodulator/biologic therapy. These refractory patients had >12 fold increased annual median healthcare charges compared with control IBD patients. Early identification of IBD patients at risk of short bowel syndrome and improving medical treatment options to prevent extensive resections and the need for long-term TPN/IVF support is warranted.
**25-R Poster:** Comparison of Circulating Tumor DNA (ctDNA) sequencing and Tumor-Based Genotyping for detection of EGFR mutations in Non-Small Cell Lung Cancer (NSCLC)

**Presenter:** Allen Li, Resident Medicine  
**Research Interest:** Clinical Medicine

**Mentors:** Liza Villaruz MD, Timothy Burns MD  
**Funding Source:** NIH Core Grant (P30 CA147904)

**Authors:** Allen Li MD, Sanja Dacic MD, Timothy Burns MD, Mark Socinski MD, Liza Villaruz MD

**Introduction:** Therapy for NSCLC is based on detection of actionable oncogenic drivers. Conventionally, targetable mutations are detected by tissue biopsy, which may be insufficient for molecular testing. Repeat biopsy is often required at the time of disease progression. Guardant360™ (G360) utilizes digital next-generation sequencing (NGS) to analyze ctDNA in plasma. Limited data exists on clinical outcomes of 3rd generation EGFR tyrosine kinase inhibitors (TKIs) against T790M-mediated resistance detected by digital NGS in ctDNA. We hypothesize that G360 has high concordance in detecting actionable oncogenic drivers and similar clinical outcomes compared with tumor-based genotyping.

**Methods:** G360 (Guardant Health, Inc.) was performed in 20 advanced NSCLC patients (pts) with matched tumor-based genotyping by either Sanger sequencing (N=10) or Ion Torrent ApliSeq v.2 NGS (N=10; Life Technologies, Fisher Scientific). Matched genotypes were done at diagnosis (N=12) or at time of acquired resistance (N=8). Sensitivity, specificity, and response to EGFR TKIs (RECIST V1.1) were determined. Overall survival (OS) and progression-free survival (PFS) were analyzed by Kaplan-Meier method. Objective response rates (ORR) were calculated by MedCalc(r) software.

**Results:** Compared with tumor-based testing, G360 has high concordance for EGFR exon 19 deletion, T790M and L858R (90%, 85% and 100%, respectively) and high specificity (100%, 93.3%, and 100%, respectively). OS of pts with T790M or L858R were similar between those detected by G360 and by tumor-based testing (p>0.99). Pts who received 3rd generation EGFR TKIs (4 osimertinib, 1 PF-06747775) after detected T790M in plasma (N=4) had similar ORR (50% vs 25% with difference of 25%, 95% CI (-0.45 to 0.75)) and median PFS (7.5 vs 6.0 mos, p=0.63) as those detected by tumor-based testing (N=4).

**Conclusion:** G360 showed high concordance for EGFR actionable mutations. Clinical outcomes of 3rd generation EGFR TKI treatment in T790M+ disease were similar between those detected by G360 and those detected by tumor testing. G360 represents a viable option for pts who are not candidates for solid tumor biopsies.
**26-R Poster:** Autoantibodies Predict Long Term Survival in Myositis Associated Interstitial Lung Disease

**Presenter:** Silvia Martinez, Resident  
**Research Interest:** Clinical Rheumatology and Clinical Immunology

**Mentors:** Rohit Aggarwal MD  
**Funding Source:** None

**Authors:** Silvia Martinez MD, Chester Oddis MD, Rohit Aggarwal MD

**Introduction:** Interstitial lung disease (ILD) is the major cause of morbidity and mortality in adult Polymyositis (PM) and dermatomyositis (DM). Myositis associated autoantibodies (MAA) are very specific for PM/DM and are associated with unique clinical phenotypes and outcomes in myositis. Particularly, antibodies to various tRNA synthetase call anti-synthetase antibodies (Anti-synAb such as anti-Jo1) are associated with high rates of ILD. Aim of the study is to determine survival outcomes of myositis associated ILD (MA-ILD) and evaluate difference in outcomes by autoantibody subsets.

**Methods:** Patients with myositis with ILD or patients with anti-synthetase syndrome with ILD were identified from The University of Pittsburgh CTD Registry which encompasses more than three decades prospective data and a serum sample repository collected on consecutive outpatients and inpatients with various autoimmune diseases evaluated at the University of Pittsburgh. PM and DM were defined as patients meeting probable or definite Bohan and Peter classification criteria and anti-synthetase syndrome patients were defined as having one of the 8 recognized anti-synthetase autoantibodies (i.e. anti-Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo and Tyr). Dead or transplant status was evaluated from the database or electronic medical record. Kaplan Meier curve and log rank test were used to determine survival rates and differences between various autoantibody groups. Cox Proportional Hazards model was used to determine survival differences after controlling for covariates like age at diagnosis, gender, ethnicity and baseline FVC%.

**Results:** 369 patients were identified as having MA-ILD, of these 306 had positive autoantibodies (82.9%). Overall, 62% (231) had myositis associated autoantibodies (MAA’s) and 54% (198/369) patients, had anti-synthetase syndrome. The most common antibody was anti-Jo-1 with 124 patients (40.5%). Overall 5 and 10 year survival of MA-ILD was 80.0% at 5 years and 71.8% at 10 years. Patients with MAA had better survival as compared to patients without autoantibodies (5 and 10 years survival 80.0% vs. 71.5%; 71.8% vs. 58.3%, p = 0.003). Among the patients with MAA, anti-synthetase patients had better survival as compared to non-synthetetase antibodies (5 and 10 years survival 80.3% vs. 72.8%; 72.7% vs. 60.9%, P = 0.004). Among the patients with anti-synthetase patients with Jo-1 had better survival than patients without anti-Jo-1 antibody (5 and 10 years survival 85.5% vs. 71.6%; 76.6% vs. 64.9%, P = 0.04).

**Conclusion:** Patients with myositis antibodies, especially anti-synthetase have better survival rates as compared to patients without autoantibodies. Among anti-synthetase syndrome Jo-1 positivity had better survival. Myositis-associated antibodies are predictors of long-term prognosis.
**27-R Poster:** The Impact of Cognitive Function on Adherence to Hydroxyurea Therapy in Patients with Sickle Cell Disease

**Presenter:** Cristina Merkhofer, Resident Medicine

**Research Interest:** Clinical

**Mentors:** Enrico Novelli MD, MS

**Funding Source:** None

**Authors:** Cristina Merkhofer MD, MHS, Susan Sylvester MS, BSN, RN, CCM, Michelle Zmuda BS, Jude Jonassaint RN, Laura De Castro MD, Gregory Kato MD, Meryl Butters PhD, Enrico Novelli MD, MS

**Introduction:** Cognitive impairment is a serious complication of sickle cell disease (SCD). While it adversely affects school performance and development in children, its impact in adults is unknown. Poor disease self-management and adherence to hydroxyurea are problems in SCD and are likely impacted by cognitive impairment. We hypothesized that lower cognitive function is associated with worse adherence to hydroxyurea therapy in adults with SCD.

**Methods:** We designed a cross-sectional study of patients with SCD from the UPMC Adult Sickle Cell Clinic. Patients who underwent neurocognitive testing between 2011-2016 and whose adherence to hydroxyurea therapy has been monitored by a dedicated clinical nurse were included. We explored the association between performance on four tests of verbal learning, memory and executive function—the Hopkins Verbal Learning Test-Revised (HVLT-R) retention, HVLT-R total recall, Delis-Kaplan Executive Function System Trail Making Condition 4 vs. 5, and Color Word Condition 3—and the most recent adherence data available. Adherence measures included the biomarkers red blood cell corpuscular volume (MCV) and percentage of fetal hemoglobin (HbF), and the patient’s self-report of adherence categorized as “good” (= 80% adherence) or “less-than-good” (< 80% adherence). Differences between groups were compared by 2-sided t-test or chi-square tests.

**Results:** Study participants (n=48) had a mean age of 35.2 years, were predominantly female (58.3%), and 72.9% had a HbSS or HbS/ß0 thalassemia phenotype. There was no difference between the two adherence groups with regard to these characteristics. The mean MCV was significantly higher in the “good” adherence group (102.3 ± 15.0 vs. 89.1 ± 11.5 fl, p=0.005), corroborating patients’ self-report. We observed a statistically significant positive correlation between the HVLT-R retention score and MCV even after adjustment for demographic characteristics (Pearson r=0.309, p=0.033). Similar correlations between HVLT-R total recall and MCV (Pearson r=0.269, p=0.085), and between HVLT-R retention and HbF percentage were observed (Pearson r=0.260, p=0.081). The mean HVLT-R retention and HVLT-R total recall scores were higher in the “good” adherence group (80.1% ± 27% vs. 64.9% ± 33%, and 41.9% ± 14% vs. 34.1% ± 13%), although the difference was not significant.

**Conclusion:** Our study suggests that adherence to hydroxyurea in adults with SCD might be affected by impairment in episodic memory, as measured through HVLT-R retention, with similar patterns by HVLT-R total recall. These results suggest that a brief, targeted neurocognitive assessment should be considered as part of any strategy to improve adherence to hydroxyurea and other therapies in patients with SCD.
28-R Poster: Comparison of Extra Cardiac Tracer Activity Between Standard Regadenoson (StdReg) and Regadenoson on the Treadmill (ExReg) Stress Protocols

Presenter: Ricardo Nieves, Resident Medicine
Research Interest: Clinical Medicine

Mentors: Prem Soman MD, PhD
Funding Source: None

Authors: Ricardo Nieves MD, Ahmad Masri MD, Andrew Althouse PhD, Prem Soman MD, PhD

Introduction: Low level physical activity with vasodilator stress is believed to reduce extra cardiac tracer uptake and improve image quality. Hypothetically, Regadenoson (Reg) given during the recovery phase to convert an inadequate exercise to pharmacological stress test should result in images with less background activity as compared to standard regadenoson stress.

Methods: We evaluated a total of 200 consecutive patients (age 64.9±12 years, 65% male) who underwent either ExReg (n=100, Reg given 3 min in recovery) or StdReg (n=100). Blinded readers scored extra cardiac (EC) activity on stress scans as: (I)= minimal, (II)= present, but not interfering with image interpretation, and (III)= present and interfering with image interpretation.

Results: Marked EC activity affecting image interpretation was more prevalent on StdReg studies than ExReg studies (34% vs. 25%). In multivariable analysis adjusting for age, gender, and effective dose; there was significantly higher odds of interfering EC activity in StdReg as compared to ExReg (OR=1.82, 95% CI 1.06-3.14, p=0.029). Inter-observer agreement on EC rating was 90% (Kappa = 0.84).

Conclusion: Improved image quality is an added advantage of ExReg, which allows easy conversion of exercise to pharm stress. This allows for a lower threshold for attempting exercise stress in patients with uncertain functional capacity.
29-R Poster: Rothman Index at Hospital Admission has Good Predictive Value for Mortality in a Large Academic Medical Center

Presenter: Carlos Pacheco, Resident Medicine

Research Interest: Clinical Medicine

Mentors: Raghavan Murugan MD, MS, FRCP

Funding Source: None

Authors: Carlos Pacheco MD, Carol Scholle MSN, RN, Robin Evans MSN, RN, Colleen Cochenour MSN, RN-BC, Darlene Lovasik MN, RN, CCRN-K, Richard Simmons MD, Raghavan Murugan MD, MS, FRCP

Introduction: The Rothman Index (RI) is a severity of illness score designed for early detection of patients who are clinically deteriorating in a hospital setting. The RI is unique in that it incorporates 26 different variables including vital signs, laboratory data and nursing assessments that are continually updated in the electronic medical record.

Methods: We analyzed a large dataset of patients admitted to the University of Pittsburgh Medical Center, a tertiary care academic medical center, from March 2014 – December 2014, excluding those who were directly admitted to the ICU. We examined predictive value of first RI obtained in the first 24 hours of hospital admission for rapid response team calls including crisis (Condition C); cardiac or pulmonary arrest (Condition A); ICU transfer; or hospital mortality, using Receiver Operating Characteristic Curve (ROC) Analysis.

Results: Of 24,060 patients admitted to the floor, 3.02% had Condition C, 0.17% Condition A, 12.28% were transferred to ICU, and 1.39% died. The first RI value was lower among patients with the events compared to those without (Table 1). The RI value had a good predictive value for hospital mortality and modest predictive value for other events. The combined predictive value of the first RI for all events were only modest (ROC, 0.74, 95%CI, 0.72 – 0.75, P<0.001).Table 1Type of Event|First RI Value, Mean (SD)|ROC (95%CI)|P Value|Patients with events|Patients without events||Condition C|59.5 (19.6)|73.2 (16.8)|0.71 (0.69-0.73)|<0.001|Condition A|56.2 (23.1)|72.8 (17.1)|0.72 (0.64-0.80)|<0.001|ICU transfer|55.9 (24.2)|75.1 (14.3)|0.73 (0.72-0.74)|<0.001|Death|42.5 (25.0)|73.2 (76.5)|0.84 (0.81-0.86)|<0.001

Conclusion: Among patients hospitalized to a large academic medical center, the first RI had a good predictive value for mortality and modest predictive value for crisis, cardiopulmonary arrest and ICU transfer.
**30-R Poster:** The Diabetic Eye: Diabetic Retinopathy Screening in a resident operated clinic  

**Presenter:** Shrina Parekh, Resident  
**Medicine**  
**Research Interest:** Clinical  

**Mentors:** None  
**Funding Source:** None  

**Authors:** Shrina Parekh MD, Anu Saini MD, Prerna Sharma MD  

**Introduction:** At UPMC, EMR tracked data indicates that Mercy Health Center has a low rate of 27% documented diabetic eye exams. Our objective was to perform a retrospective chart review of diabetic patients at the Mercy Health Center to study the factors affecting non-compliance and lack of referral.

**Methods:** We studied all patients who had been seen at least 3 times by a continuity resident-physician between 2013-2016 (N=138). We compared gender, HgbA1c, ethnicity and history of previous retinopathy in two groups- patients screened versus not screened and patients referred versus not referred by the PCP. A Chi-squared test was used to test the clinical significance (p value less that 0.05) and difference among gender, HbA1c > 7, ethnicity as well as history of retinopathy with referral and screening.

**Results:** We saw no clinically significant difference among patients whose A1c value was above or below 7 within subgroup of screened versus non screened (p value 0.21) and referred versus non referred (p value 0.98). Moreover, data also revealed that ethnically Black patients had a higher rate of failure to be screened. We also noted that about 31% of screened patients had a history of retinopathy whereas amongst subgroup of non-screened patients only 4% had history of retinopathy (p value 0.00001). 40 out of 99 people were referred but failed to get screened and amongst those who were not screened, 12 patients had documentation explaining that patient already has been following with eye clinic.

**Conclusion:** Data collection reveals that factors including HgbA1c and Gender did not appear to be significantly associated with being more likely to screened or referred by PCP. It was noted that ethnicity had association with screening of retinopathy. Black patients had lower rate of screening in comparison to other ethnicity. More importantly, our data analysis revealed that patients who had history of diabetic retinopathy were more likely to be screened (p value less than 0.05). It maybe that patients who are aware of their previous retinopathy history are more likely to follow up with an ophthalmologist and do regular eye exams. This data can help our Residents understand the motivational factors that affect retinopathy screening rates and follow up in their patient population. Emphasis can be given to patients who do not have history of retinopathy especially, so that such future adverse event can be prevented.
32-R Poster: Hiding in plain sight: Recognition and management of obesity in NAFLD patients by Primary Care Physicians and Gastroenterologists

Presenter: Krupa Patel, Resident Medicine

Research Interest: Clinical

Mentors: Jaideep Behari MD

Funding Source: None

Authors: Krupa Patell MD, Jaideep Behari MD

Introduction: NAFLD is closely associated with obesity, metabolic syndrome and diabetes. Weight loss is an integral aspect of NAFLD management, yet there are few guidelines on optimum ways to achieve this goal. We hypothesized that embedded obesity is NAFLD patients is under recognized and undertreated.

Methods: This was a retrospective analysis of 50 patients referred to a subspeciality liver clinic for evaluation of NAFLD. Clinical and demographic parameters were extracted. We reviewed the pre-referral PCP note for documentation of obesity, treatment options selected for management of obesity, recognition of obesity by the subspecialist, and treatment option addressed by subspecialists treating NAFLD over 1 year from their first visit.

Results: Of the 50 new referrals for NAFLD many were excluded from the study given known cirrhosis at first clinic visit and prior history of gastric bypass. In those not excluded, reference to BMI, waist circumference or other measures of adiposity was found in 72%, 0%, and 0% of patients with BMI-based cutoffs. Of the patients with BMI over 25, general weight loss advice was provided by subspecialists in 90% of patients and no recommendations was made about weight or diet management in others. In terms of treatment options selected, 14% were referred to a dietician for nutritional counseling, none of the patients were referred to exercise physiologist, prescription for exercise, or weight loss drugs. Only 9% of patients were given surgical referrals of weight loss surgery. Factors associated with recognition of obesity were BMI, gender, and factors associated with referral for any weight loss treatment was only BMI.

Conclusion: In this large cohort of patients referred for subspeciality care for NAFLD, embedded obesity was common but under recognized and undertreated. Our results support better education and interventions for obesity in patients with NAFLD.
**33-R Poster:** Blood Sugar Control at Discharge And Its Association with Hospital Readmissions

**Presenter:** Preethi Polavarapu, Resident
**Research Interest:** Clinical Medicine

**Mentors:** Sann Yu Mon MD
**Funding Source:** None

**Authors:** Preethi Polavarapu MD, Sann Yu Mon MD

**Introduction:** We would like to study the effect of blood sugars during discharge on the readmission of the patient.

**Methods:** We have performed a cohort study on hospitalized diabetic patients admitted to UPMC McKeesport hospital between 01/01/2016 to 06/01/2016. We collected an average 24-hour blood sugar from 50 patients prior to discharge and defined inadequate glycemic control as a binary outcome greater than 200 mg/dl. The outcome is the inpatient hospital readmissions within 90 days after discharge. We have divided patients into two groups based on average discharge blood sugar into group one (G1) <200 mg/dl, and group two (G2) discharge blood sugar >200 mg/dl. We have also collected the data on age, sex and body mass index (BMI) at primary hospitalization, and length of initial hospital stay and analyzed its association between inadequate glycemic control and the hospital readmissions.

**Results:** Results: Of 50 patients, n=36 (72%) had an adequate (G1) and n=14 (28%) had an inadequate glycemic control at discharge (G2). Mean age, BMI, and length of hospital stay are similar between G1 and G2 (63.3 yrs, 34.3 kg/m2, 6.6 days in G1 vs 63.6 yrs, 28.9 kg/m2, 4.7 days in G2 respectively). Hospital readmission rates are higher in G2 (26 readmissions for 14 patients, 1.8 readmissions per patient) than G1 (40 readmissions for 36 patients, 1.1 readmissions per patient).

**Conclusion:** This study suggests that inadequate inpatient glycemic management could lead to short-term hospital readmissions due to clinical morbidity. Safe and effective protocol-driven inpatient strategies are needed to improve clinical outcomes.
**34-R Poster:** Attitudes towards tissue donation for rapid autopsy among community and academic oncologists

**Presenter:** Padma Rajagopal, Resident 
**Research Interest:** Clinical Hematology/Oncology

**Mentors:** Shannon Puhalla MD, Adrian Lee PhD  
**Funding Source:** K08

**Authors:** Padma Rajagopal MD, Adrian Lee PhD, Shannon Puhalla MD

**Introduction:** Rapid autopsy (RA) refers to the recently developed practice of obtaining research tissue within 2-6 hours following the death of a patient. Such tissue can offer insights into the genomic and proteomic evolution of metastatic disease and possible novel therapeutic targets. Although patients generally have positive attitudes towards RA, RA programs have not been widely established by oncologists at healthcare centers with these capabilities.

**Methods:** To identify barriers to our adoption of an RA program, we conducted a 21-item web-based survey of academic and community oncologists in a single institution with regard to knowledge, attitudes and concerns about RA.

**Results:** Twenty-six physicians completed the study out of a possible 98 respondents, with 50% in academic practice and 50% in community practice. 46% were not aware of RA prior to the survey. None of the community physicians had experience with patient tissue donations of any kind. In completing the survey, 85% were willing to ask future patients about participating in RA. 58% of oncologists cited lack of awareness as their primary barrier to participation, while 31% reported discomfort in discussing rapid autopsy with patients or concern about the doctor-patient relationship. A minority of physicians had ethical concerns about the practice. The most popular strategies for increasing awareness of the RA program included distributing informational pamphlets to patients, using a third-party advocate or a discussion with the patient's primary oncologist or NP. 92% of those surveyed stated that being aware of patient interest would make them much more likely to recommend RA to patients.

**Conclusion:** Our study is among the first to clarify barriers among oncologists, particularly community oncologists, to establishing RA programs and suggests that increased information alone with clarification of patient perceptions could provide substantial progress in developing RA programs at tertiary healthcare centers and recruiting patients to these programs.
35-R Poster: HIV Infection Is an Independent Risk Factor for Decreased Six Minute Walk Test Distance

Presenter: Thomas Robertson, Resident Medicine

Research Interest: Clinical

Mentors: Allison Morris MD, MS

Funding Source: None

Authors: Thomas Robertson MD, Seyed Nouriaie MD, Kristina Crothers MD, Cathy Kessinger RN, Nicolas Leo BS, Deborah McMahon MD, Lawrence Kingsley DrPH, Ruth Greenblatt MD, Laurence Huang MD, Alison Morris MD, MS

Introduction: Ambulatory function predicts morbidity and mortality and may be influenced by pulmonary and cardiovascular dysfunction. Given the high prevalence of these co-morbidities, HIV-infected individuals may have impaired 6-minute walk test (6-MWT) distance. A prior study of HIV-infected veterans did not show an independent effect of HIV on 6-MWT distance, but found a relationship with FEV1. The aim of this study was to determine the independent effect of HIV on 6-MWT distance in a diverse cohort and to identify clinical and demographic variables associated with 6-minute walk distance.

Methods: We analyzed a cross-sectional sample of HIV-infected and HIV-uninfected individuals enrolled from 2014-2016 in 2 clinical centers of the University of Pittsburgh HIV Lung Research Cohort. Participants completed a 6-MWT, spirometry and diffusing capacity for carbon monoxide (DLco) adjusted for hemoglobin and carboxyhemoglobin, modified Medical Research Council (MMRC) dyspnea scale, and St. George’s Respiratory Questionnaire (SGRQ) and were assessed for smoking history, HIV viral load, CD4 count and anti-retroviral therapy (ART) use. Multivariate linear regression analysis was used to determine predictors of 6MWT in HIV-infected and HIV-uninfected participants.

Results: A total of 280 HIV-infected and 130 HIV-uninfected participants were included. Mean age was 52 years, 40% were female, 51% were African-American, and mean pack-year smoking history was 7.1. The average 6-MWT distance for HIV-uninfected participants was 463 meters versus 431 meters for HIV-infected participants (p = 0.0001). After adjusting for confounders, HIV status remained an independent risk factor for decreased 6-MWT (b = -.25.9, p = 0.001). Risk factors associated with decreased 6-MWT distance differed in HIV-infected versus HIV-uninfected participants (Table 1). Lower FVC, used as a surrogate for TLC, was related to decreased 6-MWT distance in HIV-infected, but not HIV-uninfected individuals, and lower DLco% predicted was associated with decreased distance in both groups. FEV1% predicted was not associated with 6-MWT distance in either cohort. CD4 count and HIV viral load were not associated in HIV-infected individuals.

Conclusion: In our cohort, HIV infection is an independent predictor of decreased physical function as measured by 6MWT distance. Specific characteristics including restrictive lung function pattern, low DLco% and subjective assessments of respiratory symptoms can identify HIV-infected individuals at risk for impaired physical function. Clinical factors associated with 6MWT distance differ in HIV-infected and HIV-uninfected. Whether the decreased 6MWT distance results from direct or indirect effects of HIV or from contributions of pulmonary or cardiovascular disease or other processes is unknown.
36-R Poster: Low Dietary Fiber Intake in Inflammatory Bowel Disease is Associated With Active Disease and Poor Quality of Life

Presenter: Sinthana Umakanthan, Resident Medicine

Research Interest: Clinical Medicine

Mentors: David Binion MD

Funding Source: None

Authors: Sinthana Umakanthan DO, Alyce Anderson PGY-III, Dimitry Babichenko MSIS, Claudia Ramos-Rivers MD, Benjamin Click MD, Ioannis Koutroubakis MD, William Rivers RN, BSN, Jana Hashash MD, Michael Dunn MD, Marc Schwartz MD, Jason Swoger MD, Arthur Barrie III MD, Miguel D. Regueiro, MD

Introduction: It has been suggested that dietary fiber intake can influence the gastrointestinal microbiota and the development of inflammatory bowel disease (IBD). However, few studies have examined fermentable fiber intake and its role in IBD patients. We aimed to determine the relationship between dietary fiber intake and IBD severity as well as disease-related quality of life.

Methods: We prospectively collected food frequency data from patients enrolled in a prospective IBD natural history registry. Questionnaires were collected during outpatient visits. Daily grams of dietary fiber were calculated using the PhenX Toolkit protocol. Daily fiber intake was categorized as 20g (high). Fiber intake groups were compared to same day inflammatory biomarkers [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)], quality of life metrics [short inflammatory bowel disease questionnaire (SIBDQ)], and disease clinical activity indices such as the Harvey Bradshaw Index for Crohn's disease (=5 active disease), and Ulcerative Colitis Activity Index (=4 active disease). We used parametric and non-parametric statistical analyses as well as logistic regression to analyze the association between fiber, disease activity, and quality of life.

Results: A total of 601 patients were included (58% female; 69% Crohn's disease, 28% ulcerative colitis, 2% IBD unclassified). Overall, IBD patients consumed less than half (48.5 ± 19.4%) of the recommended dietary intake. The majority (61%) of patients had moderate fiber intake and 28% had low intake. Dietary fiber intake was significantly associated with BMI (p=0.02), patient reported total SIBDQ scores (high: 55, moderate: 52, low: 48, p=0.004), and abdominal pain subscores (high: 5.0, moderate: 5.3, low: 5.9, p=0.005). Patients with high dietary fiber intake were less likely to have active disease (Odds Ratio (OR): 0.33; 95% CI: 0.16-0.66; p=0.002) compared to patients with low dietary fiber intake. Laboratory measures of inflammation were not statistically different between fiber intake groups.

Conclusion: Overall, IBD patients are consuming less than the recommended amount of dietary fiber. Low dietary fiber intake in IBD patients is associated with poor health related quality of life and worse clinical disease activity.
37-R Poster: The Differential Effects of Gender on Mood symptoms, Health-related Quality of Life, Social Support, and Disease Severity Among Patients with Systolic Heart Failure

Presenter: Anam Waheed, Resident Medicine

Research Interest: Clinical Medicine

Mentors: Bruce Rollman MD, MPH

Funding Source: None

Authors: Anam Waheed MD, Emily Guhl MD, Kaleab Abebe PhD, Yan Huang MAS, Amy Anderson MS, Bruce Rollman MD, MPH

Introduction: Heart failure (HF) affects nearly 6 million Americans, ranking among the most prevalent cardiovascular disorders. Although gender moderates the course of many diseases, little is known about the differential effects of gender in systolic HF (sHF). We examine its effects among patients enrolled in the NIH-funded Hopeful Heart Trial, which is exploring the impact of treating depression in patients with sHF.

Methods: We screened patients with sHF (EF <45%) and NYHA class II-IV symptoms at 8 Pittsburgh hospitals, for depression with the Patient Health Questionnaire (PHQ-2) just prior to discharge and telephoned them 2 weeks later to administer the PHQ-9. Protocol-eligible patients with a positive PHQ-2 screen and 10 on the PHQ-9 were randomized to either our depression intervention or usual care (“depressed”); while a randomly selected cohort of patients with a negative PHQ-2 screen and <5 on the follow-up PHQ-9 were assigned to our control group (“non-depressed”). We collected sociodemographic and clinical information by patient self-report and chart review at baseline, and assessed mental and physical health-related quality of life (HRQoL) using the SF-12 MCS and PCS, respectively; and social support using the ENRICHD Social Support Index (ESSI) at 2 week follow-up. Significant differences in patients’ characteristics by gender were evaluated through student’s t-test or chi-square test.

Results: From 3/14-11/16 we enrolled 545 patients with systolic HF: 44% female (F), 56% male (M). Demographic variables followed identical distribution patterns for both genders, with overall mean age 63.5 years, and about 70% of both genders being Caucasian. The prevalence of comorbidities in both genders was also similar, specifically hypertension (F:81%, M:85%, p:0.205), diabetes (F:49%, M:51%, p:0.528), depression (F:33%, M:32%, p:0.645), anxiety (F:7%, M:5%, p:0.645), both depression and anxiety (F:31%, M:29%, p:0.645). Mean levels of social support assessed by the ESSI scale (F:27.3, M:27.1, p:0.778) and HRQoL assessed by mean SF score (M:44, F:43.9, p:0.942) were also similar in both. Cardiac function measured by TTE also revealed similar distributions with mean EF 28.2% in females (range 19.8-36.6) and 27.1% in males (17.5-36.7). In spite of having similar degrees of objectively measured HF, women reported higher levels of HF symptoms as assessed by the NYHA categories. 58% women reported NYHA Class III symptoms and 12% reported Class IV symptoms, compared to 45% and 8% of men respectively (P<0.001).

Conclusion: Female participants in the Hopeful Heart Trial reported worse subjective HF severity by NYHA class compared to males, despite no significant baseline differences in age, race, EF, mood symptoms, HRQoL, or disease burden. Future reports from our ongoing Trial will examine the differential impact of gender on long-term HF treatment outcomes.
38-R Poster: Pulmonary Vascular Resistance Predicts Mortality in End-Stage Renal Disease Patients with Pulmonary Hypertension

Presenter: Jonathan Wolfe, Resident Research Interest: Clinical Medicine

Mentors: Prem Soman MD Funding Source: None

Authors: Jonathan Wolfe MD, Gavin Hickey MD, Andrew Althouse PhD, Michael Sharbaugh MS, Deepak Pasupula MD, Dustin Kliner MD, Michael Mathier MD, Prem Soman MD

Introduction: The multifactorial etiology of pulmonary hypertension (PH) in end-stage renal disease (ESRD) includes patients with and without elevated pulmonary vascular resistance (PVR). We explored the prognostic implication of this distinction.

Methods: We evaluated pre-transplant ESRD patients in a specialty cardio-renal clinic who underwent right heart catheterization. Demographics, clinical data, and test results were analyzed. All-cause mortality data was obtained. Mean follow up was 5.2 years.

Results: Of the 150 patients evaluated, 88 (59%) had mean PA pressure > 25 mm Hg. Of these, 70 had PVR = 3 and 18 had PVR > 3. The low PVR in the majority of patients with elevated PA pressure is attributable to high cardiac output. Thirty-four patients were transplanted, and 68 died. Survival analysis demonstrated a significant prognostic effect of an elevated PVR in patients with high mean PA pressures (HR=2.26, 95% CI 1.07-4.77, p=0.03; See Figure), while patients with high mean PA pressure and normal PVR had equivalent survival to those with normal PA pressure. The effect was modestly attenuated when adjusting for transplant, but remains notable (HR=1.86, 95% CI 0.88-3.93, p=0.10) considering the small sample size.

Conclusion: Despite the high prevalence of PH in ESRD patients, elevated PVR is rare and is a determinant of prognosis in patients with high mean PA pressures. Patients with lower PVR had survival equivalent to those with normal PA pressure.
**39-R Poster:** Does depression affect glycemic control and delivery of guideline-recommended care in patients with heart failure and diabetes

**Presenter:** Margaret Zupa, Resident Medicine

**Research Interest:** Clinical Medicine

**Mentors:** Bruce Rollman MD, MPH

**Funding Source:** None

**Authors:** Margaret Zupa MD, Kaleab Abebe PhD, Yan Huang MAS, Amy Anderson MSc, Bea Herbeck Belnap PhD, Bruce Rollman MD, MPH

**Introduction:** Heart failure (HF) and type 2 diabetes mellitus (T2DM) are common, often comorbid chronic medical conditions which demand adherence with complex treatment regimens. While clinical practice guidelines assist clinicians in providing evidence-based care, co-morbid depression may impair effective management of HF and T2DM and thereby increase afflicted individuals' morbidity and mortality. However, little is known about the impact of depression in patients with both conditions. We explored the effect of depression on glycemic and blood pressure control and delivery of guideline-recommended HF and T2DM care among patients enrolled in the NHLBI-funded Hopeful Heart Trial examining the impact of treating depression in HF patients.

**Methods:** We screened patients hospitalized with systolic HF (ejection fraction (EF) = 45%) and NYHA class II-IV symptoms for depression with the Patient Health Questionnaire (PHQ-2), and telephoned 2 weeks after discharge to administer the PHQ-9. We classified patients as depressed if they screened positive on PHQ-2 and scored ≥ 10 on the PHQ-9, and recruited a randomly sampled cohort of non-depressed subjects who screened negative on PHQ-2 and scored <5 on PHQ-9 as a control group. We collected sociodemographic information from patient self-report and abstracted the medical record for diagnoses, medication use, cardiac ejection fraction, blood pressure, and HbA1c. We used student's t-test or chi-square test, when appropriate, to compare depressed and non-depressed HF patients with T2DM.

**Results:** From 3/2014 to 11/2016, we enrolled 545 HF patients including 260 (48%) with T2DM. Depressed (N=211) and non-depressed (N=49) subjects were similar by mean age (65 years), gender (58% male), EF (28%), and marital status (45% married). Seventy-six percent of depressed patients were white compared with 55% of non-depressed; 23% of the depressed group was African American compared with 41% of non-depressed (p=0.01 for racial distribution). Critically, baseline glycemic control as measured by mean HbA1c (8.2% vs 7.7% p=0.16), systolic (126 vs 123mmHg p=0.25) and diastolic (71 vs 70 p=0.53) blood pressure, and rates of guideline-adherent prescription of ACE/ARB (63% and 69% p=0.40) and statins (80% and 73% p=0.35) were similar between depressed and non-depressed patients.

**Conclusion:** At baseline, comorbid depression was not related to the glycemic control or delivery of guideline-adherent care to patients with HF and T2DM. Further research is needed to identify practices that improve adherence with guideline-based care for medically complex patients with HF and T2DM and elucidate the long-term impact of depression on patients with these conditions.
**Poster Abstracts**

**40-R Poster:** Perceptions of Strength of Social Support Amongst Patients with Decompensated Alcohol-related Cirrhosis

**Presenter:** Patricia Ajayi-Fox, Resident Medicine  
**Research Interest:** Health Services/ Clinical Epidemiology

**Mentors:** Jaideep Behari MD, PhD  
**Funding Source:** None

**Authors:** Patricia Ajayi-Fox MD, Vanitha Swaminathan PhD, Jennifer Steel PhD, Jaideep Behari MD, PhD

**Introduction:** Achieving abstinence from alcohol use is the cornerstone of management in patients with alcoholic cirrhosis. There is an unmet need for novel approaches to treat patients with alcoholic cirrhosis and ongoing alcohol use. Prior research has suggested that social support networks may mediate the effects of Alcoholics Anonymous and other substance abuse recovery programs in individuals trying to achieve sobriety. However, there is a paucity of data on the social support structures in patients with advanced alcoholic liver disease. The aims of this study was to evaluate the perceived strength of social support in patients with decompensated alcoholic cirrhosis. We hypothesized that patients with alcohol-related cirrhosis patients have perception of poor social support, which may be a contributory factor to their alcohol abuse.

**Methods:** We utilized a prospective, cross-sectional study design. We enrolled twenty nine patients with alcohol-related cirrhosis who were admitted to the University of Pittsburgh Medical Center between July and October 2016 for cirrhosis-related complications. The patients completed a survey regarding their alcohol use, impact on their life, and individuals in their life they identified as sources of support.

**Results:** Of the 29 patients enrolled in the study, 58% reported consuming greater amounts of alcohol than intended within the past year. Interference with their family and home life related to their alcohol consumption was reported by 31% of patients. Only 21% of participants were able to identify ten people whom they interacted with on a regular basis. However, 72% of participants were able to identify five or more people they regularly interacted with in the last few weeks. Out of the people identified within their support networks, the majority were family members and close friends. Regarding questions on perception of themselves and how others view them, over 70% of respondents thought there were “definitely several people they could trust to help solve their problems”, and 89% thought there were “several people they enjoyed spending time with.” Approximately 50% of patients responded “definitely” or “probably” that they were more satisfied with their lives than other people were with theirs.

**Conclusion:** Contrary to our hypothesis, a majority of patients with decompensated alcohol-related cirrhosis had perception of good social support, although a third reported limited social support. Further research is needed to determine whether stratifying alcoholic cirrhosis patients by strength of their social support and targeting group substance abuse recovery programs towards patients with poor social support networks may increase abstinence rates.
Introduction: The Birmingham Free Clinic (BFC) in Pittsburgh, Pennsylvania provides primary care and basic acute care for over 1000 uninsured patients annually. There is limited evidence in the literature that free clinics might help reduce ED visits. We sought to assess the change in number of ED visits by patients after establishment of care at BFC.

Methods: As part of a quality improvement initiative to decrease ED visits, a retrospective review was conducted in the electronic medical record associated with BFC for patients who had a first clinic visit between March 1, 2014 and December 15, 2015. The study included 660 patients with 1940 total ED visits and 988 BFC visits. We analyzed the number of ED visits within a year prior to and a year after each patient’s initial Birmingham Free Clinic visit (BFC1), and quantified changes in number of visits. A subgroup analysis was performed by number of visits to BFC during the study period to determine if increased continuity at the free clinic was associated with any change in ED visits.

Results: Among all patients, ED visits per year increased significantly after BFC1 (1.2 to 1.7 per patient, +36.7%, p < 0.0001). This increase was driven by the group of patients with 1 or 2 visits to BFC, and was not seen in patients with 3 or more BFC visits. The group of patients with 3 or more BFC visits had a significantly greater reduction in ED visits compared to those with 1 or 2 visits (-5.2% vs. +45.0%, p < 0.0015). There was no change in proportion of visits that were on a weekend, (29.1% to 26.6%, p = NS) or on a Sunday (13.1% to 13.5%, p = NS).

Conclusion: More ED visits were noted in our population after establishment of care at BFC. Patients having a new first visit at BFC have numerous reasons to have an increase in number of ED visits (development of new medical conditions, moving into the area, or increased likelihood of going to an affiliated ED in our EMR after going to BFC). Patients with greater continuity at BFC had a greater reduction/less of an increase in ED visits than those with less continuity. This study is limited by many potential confounders; however, it does suggest that ongoing care (but not isolated visits) at a free clinic may play a role in reducing ED visits.
42-R Poster: Annual income is associated with health-related quality of life in atrial fibrillation: the Atrial Fibrillation health Literacy Information Technology Trial (AF-LITT)

Presenter: Emily Guhl, Resident Medicine
Research Interest: Health Services/ Clinical Epidemiology

Mentors: Jared Magnani MD
Funding Source: None

Authors: Emily Guhl MD, Andrew Althouse PhD, Courtney Schlusser BA, Jared Magnani MD

Introduction: Atrial fibrillation (AF) is a common cardiac arrhythmia associated with significant social and medical costs. Health-related quality of life (HRQoL) is an important benchmark in AF treatment; the adverse impact of AF on HRQoL is well demonstrated. We examined the associations of social and economic factors (annual income, education) and HRQoL in a cohort of individuals with prevalent AF. We hypothesized that decreased socioeconomic status, specifically lower annual income and decreased education, is associated with worse HRQoL in individuals with AF.

Methods: Participants with prevalent AF were recruited from an ambulatory care setting. We assessed demographics, medical history, AF treatment, medications, income, education, adherence, and health literacy. We measured annual income (<$19,000; $20,000-$34,999; $35,000-$49,999; $50,000-$74,999; $75,000-$99,999; >$100,000) and education (HS/Vocational; some college/associate's; bachelor's; graduate) as categorical variables. We used the Atrial Fibrillation Effect on QualiTy of Life (AFEQT) instrument, validated for HRQoL assessment in AF, to obtain composite and domain scores (daily activity, symptoms, treatment concern, treatment satisfaction; range for domain and composite scores, 0-100). We specifically related income and education (independent variables) to HRQoL (dependent variable). We employed the Kruskal-Wallis nonparametric tests with a p-value<0.05 as statistically significant.

Results: The total cohort included 141 participants (age 70.8±10.8, 64.5% men, 93.6% white). We observed significant differences in HRQoL by income group (p=0.046). The largest difference in HRQoL between income groups was seen in participants reporting income <$19,000 (n = 13, median AFEQT 67; IQR 40-79) and those with income >$100,000 (n = 28 median AFEQT 83; IQR 72-93). When examining AFEQT scores by domain, we identified a significant difference across groups in the daily activity domain (p=0.039) but not the treatment, satisfaction, or symptom domains. There was a particularly large effect seen between participants with income <$19,000/year and those with income >$100,00/year in the daily activity domain (median AFEQT score, 56 vs. 86). No significant associations were identified between educational level and HRQoL.

Conclusion: In this limited-sized cohort of primarily older adults with prevalent AF, we identified a strong association between income and HRQoL. Specifically, we observed that decreased income is strongly associated with worse HRQoL, most particularly with daily activities. HRQoL is a benchmark for clinical care in AF, and our results suggest that decreased socioeconomic resources contribute significantly towards adversity in individuals with AF. Further studies are essential to identify the specific mechanisms by which individuals with less economic resources and AF suffer a greater insult to HRQoL from the condition.
43-R Poster: Free clinic utilization and patient perceptions on Medicaid expansion under the Affordable Care Act within Allegheny County, Pennsylvania.

Presenter: Caroline Kensler, Resident Medicine

Research Interest: Health Services/Clinical Epidemiology

Mentors: Thuy Bui MD, William Markle MD

Funding Source: None

Authors: Veli Bakalov MD, Amy Kennedy MD, Mary Herbert MPH, Caroline Kensler MD, Laura R. Uribe MD, Michael Stegmaier PhD, Vindhya Ravulapati, Sharon E Connor PharmD, Maggie Benson MD, William Markle MD, Thuy Bui MD

Introduction: Approximately 20 million Americans have gained health insurance since the Affordable Care Act (ACA) became law in 2010. With the implementation of the ACA, uninsured rates for adults within the United States have decreased. However, more than 76,450 people in Allegheny County, Pennsylvania are still uninsured. Many may qualify for health insurance, yet little is known about the barriers to access insurance through the ACA. The objective of this study was to assess healthcare utilization and patients’ perceptions on barriers to apply for health insurance at three free clinics within Allegheny County, PA from 2013-2016.

Methods: Data on annual patient visits from 2013-2016 was obtained from the Birmingham Free Clinic, the McKeesport Free Clinic, and the Braddock Free Clinic. Medicaid utilization data on Allegheny County was obtained from the Pennsylvania Health Care Cost Containment Council (PHC4). We conducted a survey of uninsured patients at these three locations from September 2016 to February 2017. Data analysis was accomplished using Microsoft Excel and STATA-14. For data visualization we used GraphPad 6.

Results: Medical record data demonstrated a decrease in annual patient visits in all three free clinics from 2013 to 2016, with a significant decrease noted in 2015 (p=0.046). Mean decrease among all three free clinics in 2015 was 21.4% compared to a 10.4% decrease in 2014. Annual patient visits in 2015 decreased by 13.8% at Birmingham free clinic, by 27.0% at McKeesport free clinic and by 23.4% at Braddock free clinic. Data by PHC4 note a 9.5% increase in Medicaid visits in Allegheny County in 2015, in comparison to a 0.83% increase in 2014. Preliminary data from 100 patient surveys suggest that the main barriers that patients face when applying for health insurance include lack of education, high cost of health insurance, and lack of trust between health insurance providers and uninsured individuals.

Conclusion: Data suggests that the decrease in number of patient visits to free clinics in Allegheny County, PA in 2015 is associated with increased access to health care driven by the implementation of the Medicaid expansion under the ACA in early 2015. Medicaid expansion is an effective method to provide access to health care for this population. We must address barriers to access to health insurance including assisting with education regarding eligibility criteria and the application process, as well as establishing trust between the uninsured and health insurance providers.
44-R Poster: Physician clinical perspective of notifiable diseases (ND) and epidemiological data

**Presenter:** Brandon Smith, Resident Infectious Diseases

**Research Interest:** Health Services/Clinical Epidemiology

**Mentors:** Mohamed Yassin MD

**Funding Source:** None

**Authors:** Brandon Smith MD, Ismail Mohammad, Mohamed Yassin MD

**Introduction:** Notifiable disease (ND) is a powerful way of surveillance that was established in the US in the late 1800s to guide preventive efforts. Mortality morbidity weekly reports (MMWR) published by the Centers for Diseases control and prevention (CDC) are describing large nationwide data. Physicians’ practice is heavily influenced by the patient population served by the particular medical facility. Physicians’ practices serve as sentinel points of surveillance for many diseases. The goal of this study is to review epidemiological ND data from clinical physician perspective using three important ND with different modes of transmission.

**Methods:** Our Health system is the largest in Western PA with individual 18 medical centers that are classified as urban, suburban and rural. The study compared the health system data to the national data were collected from the CDC, state data from Pennsylvania Department of Health (PA-DOH) and county level data from the Allegheny County Health Department (ACHD). Tuberculosis (airborne), Salmonella (food-borne) and Syphilis (sexual transmission) were selected to represent ND that are important for broad range of medical practice. The data reviewed from 2010-2013 for the health center, national, state and county data. We normalized the data by number of admissions in hospitals and by the population of each region. We examined the difference in age, geographic location and time of the year. Statistical analysis was performed using Stata v14.1 using standard descriptive statistical methods.

**Results:** The national and state data showed steady decline of TB, Salmonella and Syphilis between 2010 to 2013. Unlike national, state and county data, the health system data showed more significant changes with more than 3 fold increase in TB and Salmonella. Urban hospitals showed increase in both Salmonella and TB. Rural facilities surprisingly showed increased rates of all three diseases with a much lesser extent. The mean age of TB and Salmonella infections were lower in urban as compared to rural and suburban. Syphilis was diagnosed in higher mean age in suburban facilities as compared to rural and urban facilities.

**Conclusion:** This study highlights the importance of detailed local data for healthcare providers. Local facility epidemiologic data are important aid to decision making for early diagnosis and management. Allocation of resources at the local level can’t be efficient without accurate local data. Physicians’ abilities to recognize the type of patients seen at a particular facility could be significantly augmented with these local data as compared to larger data over the years.
**Introduction:** Both HIV (Human Immunodeficiency Virus) and HCV (Hepatitis C Virus) are blood-borne pathogens with common risk factors for acquisition. For this reason, the PACT clinic has a substantial population of HIV/HCV co-infected patients. The past several years has seen the development of new, highly effective therapies, in the form of direct-acting antivirals (DAAs) to combat HCV, that are also compatible with most HIV anti-retroviral therapies (ART). HIV infection is independently associated with advanced liver fibrosis and cirrhosis in patients with HCV coinfection. According to current AASLD-IDSA guidelines, treatment of HCV is recommended for all patients with chronic HCV infection, except those with short life expectancies from other medical comorbidities.

**Methods:** The main goal of our project was to initiate HCV treatment among more of the HIV/HCV co-infected patients following at PACT. To achieve this goal, we sought to increase the number of HIV/HCV co-infected patients who have a Metavir score (which estimates the degree of fibrosis and inflammation of the HCV-infected liver, and is necessary to include in the prior authorization documentation for DAAs). In addition, we sought to increase the number of HIV/HCV co-infected patients who have a prior authorization for DAA therapy submitted to their insurer. From a known pool of 146 HIV/HCV-coinfected patients who have received care at the PACT clinic, we identified 56 patients who had a suppressed HIV viral load (indicating good adherence to therapy) and who had come into PACT for a medical visit in 2016. Using this pre-intervention dataset, we contacted each patient’s primary HIV care provider to assess the patient’s appropriateness for DAA treatment initiation and to offer a lab script for the necessary labs to calculate a Metavir score. At the end of a four month period, we reassessed our clinical indicators, specifically whether more HIV/HCV patients had initiated DAA therapy.

**Results:** Pre-intervention chart review showed that major barriers to initiating DAAs included patients coming to clinic appointments and patients adhering to HIV ART. Relative barriers on the part of the patient included alcohol or substance use, unstable housing, and competing priorities during the visit. Relative barriers on the part of the provider included being unsure of the most recent AASLD-IDSA guidelines.

**Conclusion:** Providing a script to obtain the labs to calculate a Metavir score and submit the documentation for a prior authorization, outside of the constraints of an office visit, provides a potential way to start more patients with complex care needs on HCV DAA therapy.
**Poster Abstracts**

**46-R Poster:** Delicate Balance Inpatient vs. Outpatient: Resident Satisfaction Survey

**Presenter:** David Chin, Resident Medicine  
**Research Interest:** Medical Education

**Mentors:** Mehrshid Kiazand MD, Mohamed Yassin MD  
**Funding Source:** None

**Authors:** David Chin MD, Warren Lee MD, Mohamed Yassin MD, Mehrshid Kiazand MD

**Introduction:** The Residency Review Committee for Internal Medicine mandates that programs “must develop models and schedules for ambulatory training that minimize conflicting inpatient and outpatient responsibilities”. However, it is important to ensure continuity of care between resident and patient, especially between elective blocks. Amending the schedule for continuity clinic will improve resident satisfaction without detriment to patient care.

**Methods:** Before intervention, residents had one half-day weekly clinic in rotations except Critical Care Medicine (CCM), and Night Medicine. We defined “Core Rotations” as Inpatient Medicine, CCM, and Night Medicine. Residents’ outpatient schedules were changed to one full clinic day (morning and afternoon sessions) during non-core rotations. A “Resident Panel” was instituted to provide focused care when the primary resident was not available. Finally, the allotted clinic appointment time for any type of patient visit was increased. Resident cohort responses were compared and analyzed using STATA 14.1 statistical software (N-1 two tailed proportions and T-Test). Pre- and post- study intervals, comparing the two consecutive academic years’ surveys were designed. Each survey included 21 online questions and was sent to residents via a secure online application in November of 2014-2015 and 2015-2016 academic years.

**Results:** From 57 residents in our program, 33 from 2014-2015 and 46 from 2015-2016 academic year participated in this survey. Increased clinic appointment time resulted in increased resident satisfaction that approached statistical significance (P=0.07). There was no significant difference in perception of patient ownership or continuity of care by provider (P =1) and quality of care patients receive (P=0.44). There was no significant (P=0.35) differences between each year’s cohort of monthly patient visits.

**Conclusion:** Although a majority of Internal Medicine training programs adopted the “X+Y” block schedule, we redesigned our continuity clinic to an inpatient/outpatient model. These changes had the greatest impact in residents’ satisfaction without sacrificing continuity of care or number of visits per month. These results highlight the importance of considering residents’ preferences when allowing clinic operations to evolve.
47-R Poster: An E-learning Module on Chronic Low Back Pain in Older Adults: Effect on Medical Resident Attitudes, Confidence, Knowledge, and Practice Patterns

Presenter: Zachary Jacobs, Resident Medicine

Research Interest: Medical Education

Mentors: Debra Weiner MD

Funding Source: Competitive Research Fund (Thomas H. Nimick, Jr.)

Authors: Zachary Jacobs MD, Michael Elnicki MD, Subashan Perera PhD, Debra Weiner MD

Introduction: Chronic low back pain (CLBP) negatively impacts the lives of millions of Americans each year, posing an enormous financial burden; this is in large part due to an inadequacy of chronic pain education. The goal of this study is to investigate the feasibility of using an online module to teach medical residents about CLBP in older adults, and to determine its impact on their attitudes, confidence, knowledge, and ability to evaluate and manage CLBP in the clinic.

Methods: All categorical internal medicine residents at the University of Pittsburgh Medical Center from 2015-2016 were assigned to intervention (N=73) or control groups (N=70) based on clinic schedule. The intervention group was instructed to complete an online, self-guided module previously developed by a panel of experts. The control group was exposed instead to the Yale "Office-Based Medicine Curriculum" on CLBP. Knowledge, attitudes and confidence were assessed pre- and post-intervention. Knowledge was assessed with 1) the KnowPain-12 survey (a validated, 12-item questionnaire), and 2) ten multiple choice CLBP-specific questions written by pain specialists. A reviewer masked to group assignment conducted a retrospective review of resident clinic encounters, rating physical exams and diagnoses as either beginner or advanced based on terms used in documentation.

Results: Survey results from pre- (N=44) and post-intervention (N=42) showed no improvement on the 10-item multiple choice test or the KnowPain-12 survey in either group (60% average on both metrics). There were tendencies for greater improvements in the intervention group compared to controls in confidence in managing fibromyalgia (2.4 to 2.9 vs 2.5 to 2.5; p=0.06) and leg length discrepancy (1.8 to 2.5 vs 1.5 to 1.9; p=0.05). Those exposed to the module were also more likely to use more advanced diagnosis codes (15% vs 5%) and physical exam documentation (62% vs 45%) compared to controls.

Conclusion: This study demonstrates the use of an online module is a feasible method for teaching medical residents about CLBP. One of the most startling findings is the paucity of knowledge amongst participants. These data highlight the importance of developing effective methods for educating clinicians about chronic pain. While the module did not lead to greater overall improvements on knowledge tests, it did lead to improved resident confidence, and greater sophistication in evaluating patients with CLBP.
Introduction: International medical service affords the opportunity to work with and provide mentorship for local physicians-in-training. However, these relationships tend to rapidly dissipate after a brief stint abroad. Similarly, local mentor-mentee relationships may also quickly diffuse once participants transition to a new roles and/or institutions. For this reason, electronic mentoring (E-mentoring) may be a useful way to complement traditional face-to-face mentoring. The aim of this study was to assess the feasibility of using a mobile application (app) to sustain pre-existing mentoring relationships between Global Health residents at the University of Pittsburgh Medical Center (UPMC) with local Malawian medical students.

Methods: In 2015, we developed a mentoring group involving UPMC Global Health residents and local medical students at the University of Malawi College of Medicine. The group met weekly for eight weeks during our stay in Malawi. After our return to our local institution we maintained these relationships using the text-messaging program WhatsApp. Each week we sent inspirational quotations and clinical pearls relevant to practice in the resource-limited setting. These quotations and pearls were tailored by each resident based on her/his in-person experiences with the Malawi residents.

Results: There are currently a total of 31 members in the WhatsApp mentoring group. From March 2016 until the present, there have been a total of 76 unique unsolicited student responses to the weekly messages. This represented an average of 10 responses per month and 3 responses to each individual teaching post. One hundred percent of the 76 student responses were positively valenced, with responses expressing gratitude, positivity, and interest in the information provided.

Conclusion: These findings suggest that it is feasible to leverage the text-messaging program Whatsapp to maintain mentor-mentee relationships that end due to distance. While we used this platform to provide weekly inspirational messages and clinical pearls with local medical students at the University of Malawi College of Medicine, the specific nature and frequency of communications can be tailored based on the particular needs of mentors and mentees. In the future, we hope to provide prompts to encourage students to pose their own clinical questions and experiences, and also to share strategies for coping with stressful situations.
**Introduction:** Narrative medicine is defined as the practice of clinical medicine using narrative competence: the skillset necessary to effectively “listen to, absorb, and be moved by the stories of illness”. Training healthcare professionals in the study of narrative has been shown to reduce clinician burnout and increase empathic tendencies, as well as improve patient satisfaction and clinical outcomes. The goal of this project is to develop a sustainable, multidisciplinary, collaborative workshop in narrative medicine which serves to cultivate empathy and promote well-being amongst healthcare professionals.

**Methods:** The workshop is open to healthcare professionals of all disciplines at the University of Pittsburgh Medical Center (UPMC). It takes place over the course of eight, hour-long, monthly sessions throughout 2016, which focus on developing a variety of narrative skills, including 1) reflective writing/storytelling; 2) close reading of literature/poetry; and 3) interpretation of film, art, and photography. The curriculum was designed to cover such themes as bearing witness to suffering, coming to terms with dying, living with chronic illness, and the isolating nature of disease, among others. Between monthly sessions, participants continue to collaborate via an online forum, where workshop leaders periodically post excerpts of prose or poetry for guided discussion, as well as prompts for reflective writing. In order to assess how the workshop impacts tendencies toward empathy, sympathy, and burnout, three validated surveys were administered to all participants prior to the first session, and will be readministered at the conclusion of the study.

**Results:** Early feedback from participants has been overwhelmingly positive. Preliminary data (N=9) from the pre-intervention surveys suggest high baseline tendencies toward empathy (mean: 52/64), perspective taking (mean: 21/28), and empathic concern (mean: 23/28), while scores for depersonalization (mean: 2.4 / 18) and emotional exhaustion (mean: 6.3/18) were both low. The outcome of the workshop is yet to be determined, but the hope is to demonstrate that our curriculum improves participant empathy and sympathy while reducing burnout.

**Conclusion:** By selecting a manageable number of key narrative concepts paired with integral healthcare themes, and by utilizing a collaborative online forum to minimize the amount of face-to-face time required, this novel curriculum demonstrates that teaching narrative medicine to medical professionals is feasible despite demanding schedules and time constraints. Moreover, it shows there exists a clear niche for this type of program, with significant interest and positive feedback even in its early stages.
**50-R Poster:** Mentorship in Malawi: A Model for Empowering Medical Students with Skills for Coping, Resilience, and Career Success

**Presenter:** Amy Kennedy, Resident Medicine  
**Research Interest:** Medical Education  
**Mentors:** Thuy Bui MD  
**Funding Source:** None  
**Authors:** Amy Kennedy MD, Zachary Jacobs MD, Henry Mwakalinga, Thuy Bui MD

**Introduction:** Mentoring programs are widely accepted as a critical component of medical education. Mentorship not only supports professional growth, it has also been shown to improve student well-being and reduce career burnout. High levels of stress are common amongst medical students across the globe, especially for those practicing in resource-limited settings. At the University of Malawi College of Medicine, students have limited access to faculty mentors and have expressed a desire for more structured mentorship opportunities. The aim of this study was to assess the impact and feasibility of a mentorship program designed to improve Malawian medical students’ mechanisms for resiliency and coping, as well as to provide them with structured career counseling from local physicians.

**Methods:** Third year medical students at the University of Malawi College of Medicine were invited to participate in a weekly mentoring group led by internal medicine residents from the University of Pittsburgh Medical Center's Global Health and Underserved Populations track. The group met in an intimate classroom setting on a weekly basis for a total of eight weeks in 2015. Topics addressed included professional burnout; making mistakes; dealing with difficult supervisors; death and dying; communication and breaking bad news; as well as narrative medicine and reflective writing. Two of the six sessions focused on career counseling, with local faculty members speaking about their own careers.

**Results:** A total of 15 students participated in the mentoring group, with eight students participating on a regular basis. Students were asked to complete a survey at the conclusion of the eight weeks. On average, the students rated the group useful (4.75 out of 5), and felt comfortable sharing during the sessions (4.5 out of 5). They cited such reasons as "being listened to", the "lack of judgment", and the "shared experiences" as the most useful aspects of the mentoring group.

**Conclusion:** This study demonstrates that small-group sessions led by visiting Global Health residents can be an effective and well-received method of mentoring for Malawian medical students. Future goals include sustaining the mentorship program with local mentors and further assessing the impact of mentorship sessions on stress levels, coping ability, and career decisions.
**Poster Abstracts**

**51-R Poster: Beat Blasts: A Multicenter Study of an Electrocardiogram Email Curriculum for Medicine Residents**

**Presenter:** Andrew Klein, Resident Medicine  
**Research Interest:** Medical Education

**Mentors:** Kathryn Berlacher MD, MS  
**Funding Source:** None

**Authors:** Andrew Klein MD, Mark Berlacher MD, Jesse Doran MD, Kathryn Berlacher MD, MS

**Introduction:** The challenges of comprehensive medical education are growing. Knowledge is expanding, time is limited, and technology is evolving. New approaches that account for this shifting landscape should utilize proven strategies of adult learning. We sought to evaluate the feasibility and effectiveness of a spaced and test-enhanced email curriculum, called Beat Blasts, based on electrocardiogram (ECG) interpretation in first-year medicine residents.

**Methods:** A total of 129 first-year Internal Medicine and Medicine-Pediatric residents at 3 institutions were asked to complete a pre-test involving the interpretation of 10 ECGs and a survey regarding learner preferences and confidence with ECG interpretation. Residents were randomized either to receive the curriculum or to continue with standard training. The curriculum involved 10 ECG-based cases, each with a management-oriented multiple-choice question, sent biweekly via email from June 2016 through December 2016. A post-test was sent in December and is currently undergoing analysis.

**Results:** A total of 83 residents (64%) completed the pre-test and survey and 41 residents (32%) completed the post-test and survey. Learning preferences were similar across the three institutions, the most popular being the use of electronic question banks (81%). Time was the most commonly identified barrier to ECG learning (88%). On a scale of 1 to 5, the mean pre-test ranking for residents' confidence level in day-to-day ECG interpretation and confidence level in making diagnostic and therapeutic decisions based upon their interpretation was 2.48 (SD 0.71) and 2.12 (SD 0.77), respectively. The mean pre-test score was 15.6 (SD 3.64) out of a possible 30 points (52%). Final results, including paired analysis of test scores and resident attitudes, to come.

**Conclusion:** Residents prefer on-line, self-directed resources for learning. Beat Blasts is a simple, inexpensive, and feasible curriculum that is in line with learner preferences and may enhance ECG interpretation for first-year medicine residents.
**52-R Poster:** Connecting the Dots: A Resident-centered Approach to Teaching Practical Skills in Ambulatory Care

**Presenter:** Amy Lu, Resident Medicine

**Research Interest:** Medical Education

**Mentors:** None

**Funding Source:** None

**Authors:** Amy Lu MD, Jaishree Hariharan MD

**Introduction:** Traditional models of ambulatory training employ a top-down, front-loaded approach where residents are given short clinic orientation, introduction to EMR, and directed to see patients under faculty supervision. No formal instruction follows to ensure residents are gaining practical skills required for success, leaving residents frustrated and overwhelmed. We developed an innovative curriculum with resident-centered workshops to build practical skills to excel in ambulatory care.

**Methods:** Pre-intervention surveys were administered to 39 residents with questions directed at current confidence in completing routine clinic tasks using EMR, inter-visit care, and utilization of ancillary services. We then implemented training workshops that highlighted nuances of EMR navigation to bolster clinic efficiency, standardized documentation to improve interdisciplinary communication, and resident-centered troubleshooting of practical ambulatory problems. Sessions were developed with resident input and led by rising chief medical residents with faculty facilitators during pre-clinic conferences. We also introduced monthly team meetings where residents discuss difficult patient cases with team-based staff including clinical pharmacist, social worker, and diabetic educator. Residents were again surveyed at 6 months on the same measures queried in the pre-intervention survey.

**Results:** Twenty-six of 39 residents completed the pre-intervention survey and 25 residents completed the 6-month follow-up survey. Responses were based on a 5-point Likert scale (1-5) from “not confident” to “very confident” and Wilcoxon ranked sum test was used to evaluate the responses. Confidence in using EMR for routine clinic tasks increased (3 vs 4, p=0.012), as well as confidence in triaging telephone encounters (3 vs 4, p=0.017) and responding to test results (3 vs 4, p=0.019). Residents also reported overall increase in clinic efficiency (3 vs 3.5, p=0.029) and communication with other members of the healthcare team (3.5 vs 4, p=0.08).

**Conclusion:** Training programs need innovative approaches to prepare trainees to become confident, successful primary care physicians. Our pilot curriculum demonstrated significant improvements in confidence in EMR proficiency, team-based care, and communication after 6 months. Utilizing resident-developed, resident-led sessions at regular intervals, blends resident training with excellent patient care. We plan to formalize training to all residents, creating a culture of confidence and efficiency and stewarding resident leadership training in ambulatory care.
53-R Poster: ARE RESIDENTS PREPARED TO WORK WITH PEOPLE LIVING WITH DEMENTIA?

Presenter: Priyamvada Murali, Resident Research Interest: Medical Education
Mentors: Rollin Wright MD Funding Source: None
Authors: Priyamvada Murali MD, Rollin Wright MD, Victoria Hornyak, DPT, GCS

Introduction: Health care providers frequently encounter patients living with dementia, yet little internal medicine (IM) residency training is dedicated to teaching how to interact with and care for older adults with diminished language and processing abilities as well as challenging behaviors. A communication skills curriculum was developed to teach IM residents how to use multiple techniques to work with patients and counsel caregivers living with dementia.

Methods: The curriculum was implemented July 2016 and occurs during a required 4-week outpatient geriatrics rotation. IM residents receive an introduction to the pathophysiology of communication loss followed by meeting residents of a dementia support personal care home in Pittsburgh, PA and hands-on practice with 13 dementia communication skills. IM residents report on knowledge, comfort, and confidence in ability to work with this patient population in a pretest/posttest survey. They document five dementia encounters, identifying skills used and self-rated skill-performance. Faculty observe and rate skill performance in at least 1 encounter. At a debriefing session, residents present a dementia encounter with active role-play of skills identified. Coaching and final performance evaluations by geriatrics faculty and a dementia education specialist are completed.

Results: Fourteen residents completed the curriculum in five rotations between July and November 2016. Nine completed both surveys and reported an average cumulative improvement of 7.33% in comfort level and 24.33% in confidence in ability to work with patients living with dementia. Knowledge improved by 5.56%. Of the thirteen skills, the three most-used were: establish connection, avoid verbal diarrhea and respect space. Further statistical analyses will be completed as more data are collected. Residents’ self-rated performance will be compared with faculty-rated performance of skills.

Conclusion: Preliminary results suggest this curriculum may improve IM residents’ comfort and confidence in their ability to work with older patients and counsel families who live with cognitive, behavioral and communication challenges. Rapid cycle improvement will be conducted to examine the modest increase in knowledge.
**Introduction:** Increasingly, residents practice in patient-centered medical homes (PCMH) where care is delivered in interdisciplinary framework. However, with little exposure to outpatient system, new interns find it overwhelming to navigate the PCMH. There is surprising dearth of literature studying curricular models within this context. We developed a curriculum designed to rapidly orient interns to multiple professions, system norms, and patient challenges within their PCMH.

**Methods:** Setting and participants: 19 categorical interns of UPMC IM program. Description: Interns played the role of patients checking out of the clinic. They made "follow-up appointments" with their interdisciplinary team to complete after-visit tasks. They experienced the challenges patients may face in navigating the clinic and reflected on how best to involve the interdisciplinary team. A debrief followed, where they shared their experience, clarified staff roles, and committed to practice-changing behaviors. Evaluation: The effectiveness is currently being evaluated with pre/post surveys, using a 5-point Likert scale ("not at all confident" to "very confident"). They assessed their confidence in utilization of staff and the ability to guide patients through the local PCMH. The worksheets are being collected for qualitative analysis.

**Results:** Discussion / reflection: Preliminary data showed that prior to the curriculum, only 21% felt confident in incorporating their interdisciplinary team; only 32% routinely utilized them; and 74% did not confidently understand the patients’ challenges. The post-curriculum data collection and statistical analysis are still pending, but preliminary data shows a positive trend with more than 65% of interns feeling confident in knowing how to best incorporate their interdisciplinary team. A few common themes arose at debrief – e.g. most interns reported that the clinic felt "hectic" and "rushed" from a patient’s perspective. They brainstormed and committed to practice-changing behaviors that they will apply to their practice, such as creating a separate patient instruction sheet at the end of each visit.

**Conclusion:** This innovative pilot project highlights the need for improvement in the ambulatory training in residency, especially in the setting of PCMHs. We believe our immersive curriculum will help to close that gap in training and inspire new interns to directly apply this knowledge to their patient management.
55-R Poster: Lost Education? Reviewing patterns in diabetes education referral in outpatient primary care and endocrine clinics

Presenter: Diana Pinkhasova, Resident Medicine

Research Interest: Medical Education

Mentors: Sandra Sobel, MD

Funding Source: None

Authors: Diana Pinkhasova MD, Warren Lee MD, Shawhin Karimi MD, Sandra Sobel MD

Introduction: Diabetes management should be multidisciplinary and referrals for diabetes self-management education (DSME) and diabetes self-management support (DSMS) should be the basis of initial management. The indolent nature of diabetes makes patient education paramount to managing and preventing complications. Our primary outcome was examining the rate of utilization of our certified diabetes educators (CDE) between our academic primary care and endocrine clinics for people with uncontrolled type 1 or type 2 diabetes. Our secondary outcome was comparing changes in HbA1c between patients who received diabetes education and those who did not at 6 and 12 month follow-ups after initial CDE visit.

Methods: Data were obtained from a large, university-affiliated patient data registry using the electronic medical record to identify all patients with diabetes at two academic outpatient clinics: a primary care clinic and an endocrine clinic. All patients (age 18–80 years) with a hemoglobin A1c >8% and seen by a physician at least once during 2013 to 2015 were included. Patients receiving steroids, hemodialysis therapy, pregnant, or undergoing bariatric surgery during the study interval were excluded.

Results: Of the 138 patients, 79 were part of the primary care clinic and 59 were part of the endocrine clinic. Of the primary care patients, 51.9% were given referrals for DSME but only 21.6% followed up with a CDE. In comparison, 52.5% of the patients from the endocrine clinic were given a referral for DSME, however, only 30.5% saw one. These differences in referral or visit rates between clinics were not statistically different. For the secondary outcome, individuals who saw a CDE had a mean difference (SD) of -1.23 (2.94) between baseline A1c and A1c at 6 months. For all patients who did not see a CDE, the mean difference at 6 months was -0.546 (1.97). When comparing A1c from baseline to 12-month follow-up, the mean difference for those who saw a CDE was -1.17 (2.85) compared to -0.837 (2.04) for those who did not see a CDE. Differences were statistically significant.

Conclusion: DSME and DSMS provided by certified diabetes educators are under utilized at both of our academic primary care and endocrine clinics, but patients who attended had a greater decrease in HbA1c. We aim to raise provider awareness to services offered by CDEs and facilitate identification and referral of individuals with uncontrolled diabetes. We hope to increase the utilization of CDE services to enhance interdisciplinary management approach of individuals with uncontrolled diabetes.
56-R Poster: Letters-to-the-Editor: A Novel Scholarly Activity in Residency

Presenter: Anam Waheed, Resident Medicine
Research Interest: Medical Education

Mentors: Kathleen Mctigue MD
Funding Source: None

Authors: Konstantinos Lontos MD, Daniela Hurtado MD, Anam Waheed MD, Peter Bulova MD, Natalie Morone MD, Kathleen Mctigue MD

Introduction: In an era of rapidly produced literature, residency programs explore methods to enhance residents’ critical literature appraisal skills and ability to practice evidence-based medicine. Letters-to-the editor (LTEs) are a method of post-publication review, which complements the pre-publication peer-review process. The UPMC Internal Medicine Residency Program has two specialized tracks designed to prepare residents for careers in academic medicine: Clinical Research Track and International Scholars Track. The program leadership incorporated LTE writing into the seminar’s curriculum in academic year 2014-2015. This pilot project was implemented for PGY2 residents of these tracks.

Methods: During the academic years 2014-15 and 2015-16, 18 PGY2 residents were asked to write a LTE. At the beginning of the academic year 2016-2017, these residents were asked to complete an anonymous online survey through Qualtrics, which was completed by all participants (100%). Didactics describing the objectives, potential scientific benefits of writing LTEs, and practical tips on working with a mentor to develop a publishable letter were held. Residents were instructed to work with a mentor to write comments on a recently published manuscript, and submit their letters for publication. Subsequently, participating residents presented their letters and their experience regarding the process.

Results: The results of the survey showed a high publication rate (44%) and the publications were in predominantly high-impact journals (average impact factor 16.9). Residents reported gaining experience in scientific writing (59%), improving critical appraisal skills (53%), engaging in scientific dialogue (53%) and enhancing their knowledge through literature review (41%). Common barriers were limited timeline allowed by journals (65%), lack of experience with prior letter-writing (41%), limited expertise on the chosen topic (41%), mentor’s time limitations (35%) and limited free time because of residency training (35%). The majority of our residents wrote a letter to encourage dialogue and debate about a topic (44%), to add new information (28%) and to state an alternative point of view (28%). Most stated that probably they will write again a letter in the future (50%), while a few of them considered it a possibility (39%).

Conclusion: Our curriculum evaluation team is encouraged by the high publication rate and multiple benefits of letter writing identified by track participants, which suggest that formal training in letter writing can foster skills in public scientific discourse. Development of mentored LTEs adds value to more traditional approaches for teaching critical appraisal skill among trainees, while fostering academic interactions between residents and faculty, and helps residents engage in professional discourse about medical research. This innovation holds value as a successful example which other residency programs may elect to add to their curricula.
Session A

May 2, 2017
Biomedical Science Tower Foyer
<table>
<thead>
<tr>
<th><strong>SESSION A</strong></th>
<th><strong>Author(s)</strong></th>
<th><strong>Poster Number</strong></th>
<th><strong>Abstract</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abadjian</td>
<td>Marie-Caline</td>
<td>1-A</td>
<td>Clickable cross-bridged chelator to prepare dimeric peptide for targeted PET imaging</td>
</tr>
<tr>
<td>Abadjian</td>
<td>Marie-Caline</td>
<td>2-A</td>
<td>PET and MR imaging with 64Cu/68Ga-labeled AGuIX ultra-small nanoparticles in tumor-bearing mice</td>
</tr>
<tr>
<td>Abdelkarim</td>
<td>Islam</td>
<td>55-A</td>
<td>Poor Agreement between Transthoracic Echocardiography and Right Heart Catheterization for Assessment of Pulmonary Hypertension Severity - Clinical Applications in the TAVR Era</td>
</tr>
<tr>
<td>Adamik</td>
<td>Juraj</td>
<td>3-A</td>
<td>Targeting Multiple Roles of EZH2 Methyltransferase in Myeloma-Induced Abnormal Bone Remodeling</td>
</tr>
<tr>
<td>Ajala</td>
<td>Oluremi</td>
<td>70-A</td>
<td>Ideal Cardiovascular Health Metrics in Couples: A Community-based Population Study</td>
</tr>
<tr>
<td>Al Hashash</td>
<td>Jana</td>
<td>78-A</td>
<td>Overexpression and Hypoglycosylation of MUC1 is Associated with Endoscopic Recurrence of Post-operative Crohn's disease</td>
</tr>
<tr>
<td>Al-Bataineh</td>
<td>Mohammad</td>
<td>4-A</td>
<td>Role of Muc1 in regulating beta-catenin signaling after moderate and severe ischemic kidney injury</td>
</tr>
<tr>
<td>Alhamaydeh</td>
<td>Mohammad</td>
<td>56-A</td>
<td>The Deleterious Effects of Atrial Fibrillation in Heart Failure: Insights Using Impedance Cardiography</td>
</tr>
<tr>
<td>Barbash</td>
<td>Ian</td>
<td>71-A</td>
<td>Hospital Perceptions of Medicare’s Sepsis Quality Reporting Initiative</td>
</tr>
<tr>
<td>Belmonte</td>
<td>Frances</td>
<td>5-A</td>
<td>PIF1 helicase ablation increases diet-induced weight gain and alters whole animal metabolism</td>
</tr>
<tr>
<td>Bogdanovich</td>
<td>Tatiana</td>
<td>57-A</td>
<td>Establishment of a Volunteer Stool Donor Bank for Fecal Microbiota Transplantation</td>
</tr>
<tr>
<td>Boyd-Shiwarski</td>
<td>Cary</td>
<td>6-A</td>
<td>KS-WNK1 is required for WNK Body Formation in Response to Potassium Stress</td>
</tr>
<tr>
<td>Brzoska</td>
<td>Tomasz</td>
<td>7-A</td>
<td>Intravital analysis of acute pulmonary thromboembolism in live mice</td>
</tr>
<tr>
<td>Cavalcante</td>
<td>Joao</td>
<td>58-A</td>
<td>Prognostic Value of Right Ventricle-Pulmonary Artery Coupling in TAVR Patients - Time to Integrate the Right Side Unit</td>
</tr>
<tr>
<td>Chatterjee</td>
<td>Suman</td>
<td>11-A</td>
<td>Therapeutic targeting of ERK1/2-p90RSK-CDC25C signaling pathway overcomes</td>
</tr>
<tr>
<td>Name</td>
<td>Last Name</td>
<td>Number</td>
<td>Poster Title</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>--------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Chen</td>
<td>Jingxin</td>
<td>12-A</td>
<td>acquired resistance to Ganetespib, an Hsp90 inhibitor, in KRAS mutant NSCLC</td>
</tr>
<tr>
<td>Cheng</td>
<td>Shaoji</td>
<td>13-A</td>
<td>A gain-of-function variant at the extracellular domain core of the epithelial Na+ channel</td>
</tr>
<tr>
<td>Clarkson</td>
<td>Becky</td>
<td>79-A</td>
<td>Functional brain connectivity during urgency urinary incontinence</td>
</tr>
<tr>
<td>Coppin</td>
<td>Emilie</td>
<td>14-A</td>
<td>Myeloid cells involvement in hindlimb ischemia induced Atherosclerosis</td>
</tr>
<tr>
<td>Dalghi</td>
<td>Marianela</td>
<td>15-A</td>
<td>RAB27B requirement for stretch-regulated exocytosis in bladder umbrella cells</td>
</tr>
<tr>
<td>Davar</td>
<td>Diwakar</td>
<td>80-A</td>
<td>Phase IB Study of Pembrolizumab (Pembro) and Pegylated-interferon alfa-2b (Peg-IFN) in Advanced Melanoma (MEL)</td>
</tr>
<tr>
<td>Demko</td>
<td>John</td>
<td>81-A</td>
<td>Urinary Plasmin as a Predictor of Increased Blood Pressure and Decline in GFR in Diabetic Nephropathy</td>
</tr>
<tr>
<td>Dudekula</td>
<td>Anwar</td>
<td>59-A</td>
<td>Gastric Electrical Stimulator for Gastroparesis</td>
</tr>
<tr>
<td>Edumnds</td>
<td>Lia</td>
<td>16-A</td>
<td>Hepatic insulin sensitivity is improved in high-fat diet (HFD) fed PARKIN KO mice in association with increased hepatic AMPK activation and reduced steatosis</td>
</tr>
<tr>
<td>Fajt</td>
<td>Merritt</td>
<td>82-A</td>
<td>A Type-2 Inflammatory Background Alters the Functional Response of Airway Mast Cells</td>
</tr>
<tr>
<td>Falabella</td>
<td>Micol</td>
<td>17-A</td>
<td>G-quadruplexes in mitochondrial function and human disorders</td>
</tr>
<tr>
<td>Florentin</td>
<td>Jonathan</td>
<td>83-A</td>
<td>Inflammatory macrophage expansion in pulmonary hypertension depends upon mobilization of blood-borne monocytes</td>
</tr>
<tr>
<td>Frahm</td>
<td>Krystle</td>
<td>18-A</td>
<td>The Dexamethasone Transcriptomes in Cortical and Hypothalamic Embryonic Neural Progenitor Stem Cells</td>
</tr>
<tr>
<td>Fuschiotti</td>
<td>Patrizia</td>
<td>84-A</td>
<td>Skin-resident effector memory CD8+CD28- T cells exhibit a pro-fibrotic phenotype in patients with systemic sclerosis</td>
</tr>
<tr>
<td>Gbotosho</td>
<td>Oluwabukola</td>
<td>19-A</td>
<td>Heme Promotes Pulmonary Hypertension in SCD by Inducing Secretion of Placenta</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Poster Number</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------</td>
<td>---------------</td>
<td></td>
</tr>
<tr>
<td>Helfield</td>
<td>Growth Factor From Erythroblasts via Oxidant Response Transcription Factors</td>
<td>20-A</td>
<td></td>
</tr>
<tr>
<td>Hoji</td>
<td>Persistence of CD57+KLRG1+ Cytomegalovirus (CMV)-specific Effector CD8 T cells through the Primary, Contraction, and Chronic phase of CMV Infection is associated with Control of Relapsing CMV infection</td>
<td>86-A</td>
<td></td>
</tr>
<tr>
<td>Hortells</td>
<td>The role of telomerase and senescence in aortic valve calcification</td>
<td>21-A</td>
<td></td>
</tr>
<tr>
<td>Ikeda</td>
<td>Relaxin reverses age-related bladder fibrosis and treats underactive bladder</td>
<td>22-A</td>
<td></td>
</tr>
<tr>
<td>Jawale</td>
<td>Kidney dysfunction is associated with intestinal dysbiosis</td>
<td>24-A</td>
<td></td>
</tr>
<tr>
<td>Kagiymama</td>
<td>Reduced Global Longitudinal Strain is Associated with In-hospital Mortality in Patients with Subarachnoid Hemorrhage and Preserved Ejection Fraction</td>
<td>60-A</td>
<td></td>
</tr>
<tr>
<td>Kelly</td>
<td>Exercise protects against hypoxia-induced pulmonary vascular remodeling in mice</td>
<td>26-A</td>
<td></td>
</tr>
<tr>
<td>Koch</td>
<td>High pulmonary arterial pressures are associated with decreased microbial nitrate metabolism in the mouth</td>
<td>87-A</td>
<td></td>
</tr>
<tr>
<td>Kohli</td>
<td>Does formal training in medical education and professional development lead to better career outcomes for clinician educators? A survey study of a degree granting program in medical education</td>
<td>75-A</td>
<td></td>
</tr>
<tr>
<td>Kotlarczyk</td>
<td>Early changes in bone turnover markers are associated with longer-term changes in bone mineral density but not microstructure in frail elderly women</td>
<td>61-A</td>
<td></td>
</tr>
<tr>
<td>Kotlarczyk</td>
<td>Fracture liaison service in an open health care system and changes in post-fracture management</td>
<td>62-A</td>
<td></td>
</tr>
<tr>
<td>Lawani</td>
<td>Associations between Peripheral Blood Monocyte Surface Markers and Pulmonary Dysfunction in HIV-Infected Individuals</td>
<td>88-A</td>
<td></td>
</tr>
<tr>
<td>Lawani</td>
<td>Associations between T Cell Exhaustion and Immunosenescence in HIV-associated Pulmonary Dysfunction</td>
<td>89-A</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>First Name</td>
<td>Age</td>
<td>Poster Code</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>-----</td>
<td>-------------</td>
</tr>
<tr>
<td>Lawani</td>
<td>Mariam</td>
<td>90</td>
<td>90-A</td>
</tr>
<tr>
<td>Li</td>
<td>Xiaoyun</td>
<td>27</td>
<td>27-A</td>
</tr>
<tr>
<td>Liang</td>
<td>Kelly</td>
<td>63</td>
<td>63-A</td>
</tr>
<tr>
<td>Liang</td>
<td>Kimberly</td>
<td>64</td>
<td>64-A</td>
</tr>
<tr>
<td>Ling</td>
<td>Xiaoxi</td>
<td>28</td>
<td>28-A</td>
</tr>
<tr>
<td>Londino</td>
<td>James</td>
<td>29</td>
<td>29-A</td>
</tr>
<tr>
<td>Lu</td>
<td>Canying</td>
<td>30</td>
<td>30-A</td>
</tr>
<tr>
<td>Majumder</td>
<td>Saikat</td>
<td>31</td>
<td>31-A</td>
</tr>
<tr>
<td>Mburu</td>
<td>Maureen</td>
<td>91</td>
<td>91-A</td>
</tr>
<tr>
<td>McCormick</td>
<td>Kevin</td>
<td>32</td>
<td>32-A</td>
</tr>
<tr>
<td>McDonnel</td>
<td>Bronagh</td>
<td>33</td>
<td>33-A</td>
</tr>
<tr>
<td>Montalbetti</td>
<td>Nicolas</td>
<td>34</td>
<td>34-A</td>
</tr>
<tr>
<td>Namboodiri</td>
<td>Hima</td>
<td>35</td>
<td>35-A</td>
</tr>
<tr>
<td>Negi</td>
<td>Vinny</td>
<td>36</td>
<td>36-A</td>
</tr>
<tr>
<td>Nyunoya</td>
<td>Toru</td>
<td>92</td>
<td>92-A</td>
</tr>
<tr>
<td>Opeť</td>
<td>Amy</td>
<td>93</td>
<td>93-A</td>
</tr>
<tr>
<td>Author</td>
<td>Name</td>
<td>ID</td>
<td>Title</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>-----</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Parekh</td>
<td>Natasha</td>
<td>76-A</td>
<td>Effect of Multi-Site Longitudinal Quality Improvement Curriculum on Internal Medicine Resident Patient Outcomes</td>
</tr>
<tr>
<td>Penrose</td>
<td>Kerri</td>
<td>37-A</td>
<td>Does the E138A mutation in ASPIRE seroconverters affect susceptibility to Dapivirine?</td>
</tr>
<tr>
<td>Posluszny</td>
<td>Donna</td>
<td>65-A</td>
<td>Levels of Patient and Family Caregiver Anxiety and Depression Symptoms and Correlates Prior to Allogeneic Hematopoietic Cell Transplantation (HCT)</td>
</tr>
<tr>
<td>Qin</td>
<td>Shulin</td>
<td>38-A</td>
<td>Rosuvastatin reduces systemic inflammation in HIV-associated chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Radomski</td>
<td>Thomas</td>
<td>73-A</td>
<td>A Comparison of Medication-based Versus Medical Claims-based Risk Adjustment to Predict 1-year Mortality among Veterans Dually-enrolled in VA and Medicare Part D</td>
</tr>
<tr>
<td>Radomski</td>
<td>Thomas</td>
<td>74-A</td>
<td>VA Physicians’ Perspectives and Experiences Regarding Prescription Drug Monitoring Programs: A Multi-State Qualitative Study</td>
</tr>
<tr>
<td>Ramani</td>
<td>Kritika</td>
<td>39-A</td>
<td>IL-17 receptor signaling in kidney epithelial cells is important in protection against disseminated candidiasis</td>
</tr>
<tr>
<td>Raphael</td>
<td>Itay</td>
<td>40-A</td>
<td>The role of STAT3 in effector Th17 cells</td>
</tr>
<tr>
<td>Revu</td>
<td>Shankar</td>
<td>41-A</td>
<td>CD28 co-stimulation negatively regulates differentiation of human but not mouse Th17 cells</td>
</tr>
<tr>
<td>Robinson</td>
<td>Keven</td>
<td>42-A</td>
<td>Protective Mechanism for Interleukin-33 during Influenza-associated Bacterial Super-infection</td>
</tr>
<tr>
<td>Rondon-Berrios</td>
<td>Helbert</td>
<td>77-A</td>
<td>Plasma Sodium Correction Practices in Patients admitted with Hyponatremia at UPMC Presbyterian and Montefiore Hospitals during 2015</td>
</tr>
<tr>
<td>Rooney</td>
<td>James</td>
<td>43-A</td>
<td>Molecular Basis of Inhibition of Acid Sensing Ion Channels by Diminazene</td>
</tr>
<tr>
<td>Rose</td>
<td>Jason</td>
<td>94-A</td>
<td>Reversal of the toxic effects of carbon monoxide (CO) poisoning on tissue respiration through a CO scavenging molecule</td>
</tr>
<tr>
<td>Roy</td>
<td>Ankita</td>
<td>44-A</td>
<td>The aldosterone-repressible protein DCNL4 promotes WNK kinase degradation via the KLHL3/CUL3 complex</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
<td>Poster</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Sellares</td>
<td>Modified mesenchymal stem cells using miRNA transduction modifies inflammation and collagen deposition in lung fibrosis</td>
<td>95-A</td>
<td></td>
</tr>
<tr>
<td>Shah</td>
<td>Therapeutic Effects of Enteral Dextrose are Mediated by the Intestinal Incretin Hormone GIP</td>
<td>96-A</td>
<td></td>
</tr>
<tr>
<td>Shi</td>
<td>The Role of Pore-lining Residues of MEC-4 and MEC-10 in the Channel’s Response to Shear Stress</td>
<td>45-A</td>
<td></td>
</tr>
<tr>
<td>Smith</td>
<td>Importance of the physical therapist when assessing physical risk of patients targeted for home-based Cardiac Rehabilitation</td>
<td>66-A</td>
<td></td>
</tr>
<tr>
<td>Sugahara</td>
<td>Prognostic Influence of Three-Dimensional Echocardiographic Right Ventricular Remodeling and Left Ventricular Stroke Work Index in Patients with Pulmonary Hypertension</td>
<td>67-A</td>
<td></td>
</tr>
<tr>
<td>Sun</td>
<td>TBK1/IKKe Signaling Is a Novel Therapeutic Target In Multiple Myeloma-Induced Bone Disease</td>
<td>46-A</td>
<td></td>
</tr>
<tr>
<td>Sun</td>
<td>A universal Sequential Dual-Receptor-targeted Pre-Targeting (SDRPT) strategy for immuno-PET</td>
<td>97-A</td>
<td></td>
</tr>
<tr>
<td>Sun</td>
<td>Heterodimeric RGD-NGR tracer for PET imaging of angiogenesis</td>
<td>98-A</td>
<td></td>
</tr>
<tr>
<td>Sur</td>
<td>Rapamycin Inhibits Calcification: Role of TNAP and Autophagy</td>
<td>47-A</td>
<td></td>
</tr>
<tr>
<td>Tan</td>
<td>Suppression of Nrf2 Activity May Lead to AKI-to-CKD Progression</td>
<td>48-A</td>
<td></td>
</tr>
<tr>
<td>Thapa</td>
<td>Gcn511 promotes enhanced cardiac fatty acid oxidation through acetylation of mitochondrial proteins</td>
<td>49-A</td>
<td></td>
</tr>
<tr>
<td>Thomas</td>
<td>Changes in sexual function among midlife women: “I’m older... and I’m wiser”</td>
<td>68-A</td>
<td></td>
</tr>
<tr>
<td>Truschel</td>
<td>Age-related changes in lysosomal function</td>
<td>50-A</td>
<td></td>
</tr>
<tr>
<td>Tyagi</td>
<td>Poor Sleep is Associated with Recurrent Falls among Older Women in the Study of Osteoporotic Fractures</td>
<td>69-A</td>
<td></td>
</tr>
<tr>
<td>Vasamsetti</td>
<td>Effect of Myocardial Infarction on Insulin Resistance: Role of Macrophage Subsets</td>
<td>51-A</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>Palmitoylation of the Epithelial Na+ Channel affects regulation by bile acids</td>
<td>52-A</td>
<td></td>
</tr>
<tr>
<td>Whitehurst</td>
<td>Daniel</td>
<td>53-A</td>
<td>Increasing Endothelial Permeability with Ultrasound and Microbubbles for Therapeutic Delivery Applications</td>
</tr>
<tr>
<td>------------</td>
<td>--------------</td>
<td>------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Yu</td>
<td>Qiuju</td>
<td>99-A</td>
<td>Epigenetic and genetic silencing of the iron-sulfur cluster scaffold protein BOLA3 drives pulmonary vascular proliferation and vasoconstriction</td>
</tr>
<tr>
<td>Zabbarova</td>
<td>Irina</td>
<td>100-A</td>
<td>Relaxin reverses fibrosis and rescues the bladder in mice with chronic radiation cystitis</td>
</tr>
<tr>
<td>Zhang</td>
<td>Peng</td>
<td>54-A</td>
<td>Targeting GFI1 reduces osteoclastogenesis and bone resorption through integrin-dependent cytoskeleton dynamics</td>
</tr>
</tbody>
</table>
1-A Poster: Clickable cross-bridged chelator to prepare dimeric peptide for targeted PET imaging

Presenter: Marie-Caline Abadjian, Post-Doctoral Fellow  
Research Interest: Bench Cardiology

Mentors: None  
Funding Source: P30CA047904 (UPCI CCSG)

Authors: Marie-Caline Abadjian PhD, Dexing Zeng PhD, Erik C. Weiner PhD, Douglas B. Grotjahn PhD, Carolyn J. Anderson PhD

Introduction: Comparing monomeric peptides, the homodimeric peptides have significant improvements in binding affinity and pharmacokinetic performance and are attracting increased interest. However, preparation of such dimers requires complex organic chemistry and bioconjugation strategies, hindering widespread and routine utilization of promising probes for preclinical and/or clinical studies. The high degree of intrinsic rapidity, specificity and flexibility, click chemistry is an ideal synthetic tool for time-sensitive production of radiopharmaceuticals. Here, a novel click chemistry platform is developed to facilitate the preparation of chelator-conjugated dimeric peptides for PET imaging. Copper-64, an attractive positron emitter, decays by both β+ (0.653 MeV, 17.4%) and β- (0.578 MeV; 39%) particles, which enable simultaneous diagnostic PET imaging and radiotherapy. Cyclic RGD peptide has been widely investigated as an αvβ3 integrin imaging agents for early detection of cancer and/or therapeutic response monitoring. As a proof-of-concept, a 64Cu-labeled cyclic RGD homodimer was prepared for αvβ3 integrin targeted PET imaging using a novel di-azide cross-bridged chelator.

Methods: Methyl ester protected cross-bridged chelator, CB-TE2(AOMe)2A, was synthesized from L-(-)-malic acid in a multi-step synthesis and was conjugated with two acetylene-functionalized cyclo(RGDyK) peptides via copper-catalyzed click chemistry, followed by methyl group hydrolysis. 64Cu-labeled homodimer, 64Cu-CB-TE2A-(RGD)2, was evaluated for serum stability for 24h at 37°C. Competition binding assays were performed to determine binding affinity for αvβ3 integrin, and in vivo evaluation was conducted in mice bearing 4T1 tumor xenografts. The data were compared to those obtained from related mono-clicked analog CB-TE2A-RGD, prepared from a chelator (CB-TE2(AOMe)1A) containing only one azide.

Results: Two clickable chelators (CB-TE2(AOMe)2A and CB-TE2(AOMe)1A) were synthesized in overall yield of 10%, and were conjugated to cyclo(RGDK) via click chemistry in >95% yield. Dimeric peptide CB-TE2A-(RGD)2 was radiolabeled with 64Cu at 37°C for 1h, whereas 64Cu labeling of the monomer CB-TE2A-RGD needed relatively harsh conditions, at either 60°C for 1h or 90°C for 30min. Improved binding affinity was observed with the dimeric RGD peptide The IC50 of the cyclic RGD dimer and monomer were 1.0 and 2.8nM, respectively. Both 64Cu labeled radiotracers were stable in human serum, and <2% 64Cu dissociation was observed after being incubating in human serum at 37°C for 24h. Compared to the 64Cu-labeled monomer (64Cu)CB-TE2A-RGD, the dimeric (64Cu)CB-TE2A-(RGD)2 showed higher tumor uptake and signal to background ratio (such as, tumor/muscle and tumor/blood) at 4h post-injection.

Conclusion: A novel cross-bridged chelator for facile preparation of a 64Cu-labeled peptide dimer was successfully developed. Compared to 64Cu-labeled monomer, dimeric 64Cu-CB-TE2A-(RGD)2 demonstrated improved radiolabeling efficiency, in vitro binding and in vivo performance.
Introduction: The overall goal of this project is to determine tumor targeting by MRI and PET imaging with ultra-small gadolinium-based nanoparticles, AGuIX, labeled with Ga-68 and Cu-64 (AGuIX-68Ga and AGuIX@NODAGA-64Cu) in a 4T1 murine breast cancer model. These particles have capabilities to radiosensitize tumors prior to external beam irradiation, and therefore imaging will assist in guiding radiation therapy.

Methods: Radiolabeling conditions for ultra-small nanoparticles with either 68Ga or 64Cu were optimized for small animal PET imaging. Ten female BALB/c mice were injected subcutaneously above the right shoulder with 1 x 105 4T1 cells and allowed to grow to ~100-500 mm3. Two mice were imaged by MRI immediately after tail vein injection of unlabeled AGuIX nanoparticles. Four mice were imaged by PET/CT at 1, 2, 4, 24 h after injection with AGuIX@NODAGA-64Cu. Four mice were imaged by PET/CT at 1, 2, 4, 24 h after injection with AGuIX-68Ga. Biodistribution studies were done at the 24 h and 4 h time point for mice injected with AGuIX@NODAGA-64Cu and AGuIX-68Ga, respectively.

Results: The radiolabeling yields of these ultra-small nanoparticles were 81-85%. T1-weighted MRI of tumors following i.v. injection showed fast accumulation (within 10 min p.i.) and slow diffusion out of the tumor (over 30 min p.i.). The PET images showed significant accumulation in the tumor, 3.00 ± 0.53% IDmax/g for AGuIX@NODAGA-64Cu 24 h.p.i. and for 4.59 ± 1.02% IDmax/g AGuIX-68Ga 4 h.p.i. Measurement of radioactivity in major organs ex vivo of AGuIX@NODAGA-64Cu 24 h.p.i. gave tumor:muscle ratios of 10.42, and the %IDmax/g was 2.63. For AGuIX@NODAGA-64Cu, the kidney had the highest non-target tissue uptake (55.9%IDmax/g at 24 h), with relatively low liver and muscle uptake (4.17 and 0.71%IDmax/g at 24 h, respectively).

Conclusion: Radiolabeling conditions are being optimized to increase radiochemical yield. The MRI images with AGuIX and PET with AGuIX@NODA-64Cu and AGuIX-68Ga nanoparticles showed accumulation in tumors with renal clearance. Optimal nanoparticle uptake into the tumors was from 1 to 4 h post injection as determined by PET/CT imaging. Co-registering of PET and MR images are underway using AGuIX@NODAGA-64Cu nanoparticles in a 4T1 tumor mouse model.
3-A Poster: Targeting Multiple Roles of EZH2 Methyltransferase in Myeloma-Induced Abnormal Bone Remodeling

Presenter: Juraj Adamik, Post-Doctoral Fellow  
Research Interest: Bench Hematology/Oncology

Mentors: Deborah L. Galson PhD  
Funding Source: NIH

Authors: Juraj Adamik PhD, Rebecca Silbermann MD, Konstantinos Lontos MD, Peng Zhang PhD, Quanhong Sun PhD, Judy Anderson BS, G. David Roodman MD, Deborah L. Galson PhD

Introduction: Multiple myeloma (MM) patients develop osteolytic bone lesions due to hyperactivation of osteoclast precursors (OCLp). The lesions rarely heal even after therapeutic remission due to MM-induced suppression of bone marrow stromal cell (BMSC) differentiation into osteoblasts (OB). Although new therapies for MM have greatly improved progression-free survival and overall survival, to date, there are no agents that can reliably repair MM lesions.

Methods: We employed kinetic GSK126 inhibitor treatments, mRNA analyses, ChIP-qPCR, western blotting, confocal microscopy and ShRNA knockdown experiments to examine the role of EZH2 in abnormal myeloma-induced OB and OCL differentiation.

Results: EZH2, the methyltransferase subunit of Polycomb Repressive Complex 2 (PRC2), catalyzes tri-methylation of histone-3 lysine-27 (H3K27me3), which induces gene repression. We reported that MM cells induce increased EZH2 recruitment to the Runx2 gene in MM patient-derived BMSC and the murine pre-OB cell line MC4, resulting in H3K27me3-mediated repression of Runx2, leading to suppression of OB differentiation. Using GSK126, a small molecule inhibitor of EZH2 activity, we show that MM-induced epigenetic repression of Runx2 is reversible in both BMSC from MM patients and MM-treated MC4 cells, resulting in increased expression of Runx2 and RUNX2 target OB genes Ocn, Bsp, and Alpl, and rescued mineralization. In contrast, EZH2 and H3K27me3 levels are upregulated during the initial 24h of RANKL-induction, thus epigenetically silencing several OCL inhibitory factors such as MafB, Irf8 and Arg1, and permitting OCL formation. EZH2 inhibition with GSK126 or Ezh2 knockout prevented OCL formation. The presence of MM1.S-conditioned media (MMCM) only during the 3-day M-CSF expansion phase of bone marrow OCLp significantly enhanced multinucleated OCL formation. MMCM enhanced RANKL-induction of Ezh2 expression and OCL marker genes was blocked when GSK126 was present at addition of RANKL. However, when GSK126 was present during the M-CSF expansion and removed before RANKL addition, only MMCM amplification of OCL differentiation was inhibited. A novel cytoplasmic role of EZH2 methyltransferase activity during early RANKL signaling was revealed. EZH2 is required for (and GSK126 blocks) RANKL activation of the pAKT-pmTOR-pS6RP signaling axis affecting the translation ratio of the C/EBPβ-LAP and LIP isoforms, resulting in increased binding of the repressive LIP isoform to the MafB promoter, which is necessary for OCL formation.

Conclusion: Our in vitro studies suggest that in vivo GSK126 inhibition of the epigenetic modifier EZH2 may improve the osteogenic potential of MM-exposed BMSC and suppress OCL formation, and thus may prove a valuable therapeutic strategy to repair bone disease in MM patients.
Introduction: Beta-catenin signaling is activated in tubules during acute kidney injury. In tumor cells, the transmembrane glycoprotein mucin 1 (human MUC1/animal Muc1) stabilizes beta-catenin by blocking glycogen synthase kinase 3beta (GSK3beta)-mediated degradation. We reported that Muc1 plays a protective role in a mouse model of ischemia-reperfusion injury (IRI) using Muc1 KO mice and congenic control mice (AJP-Renal 2015; PMID: 25925251). We then showed that Muc1 induction during IRI was associated with increased beta-catenin levels/signaling (AJP-Renal 2016; PMID: 26739894). Xiao et al. (JASN 2016; PMID26453613) found that moderate ischemia with transient induction of beta-catenin proceeded to recovery of kidney function, while severe ischemia led to sustained activation of beta-catenin and development of kidney fibrosis. We tested the hypothesis that Muc1 modulation of beta-catenin levels accounts for protection after moderate AKI and for progression to CKD after severe AKI.

Methods: Renal proximal tubule-specific GSK3beta KO and congenic control mice were exposed to mercuric chloride (HgCl2; a potent nephrotoxin) in the absence or presence of GSK3beta inhibitor (TDZD-8). In addition, Muc1 KO and congenic control mice were subjected to moderate or severe IRI using bilateral renal pedicle clamping model.

Results: Muc1 levels were increased in the HgCl2-treated mouse kidney compared to controls, while we found more cytoplasmic Muc1 after treatment with TDZD-8. GSK3beta gene deletion in proximal tubule cells enhanced both Muc1 and beta-catenin levels after HgCl2 treatment based on IF-staining. We observed a significant sustained increase in both Muc1 (7-fold) and beta-catenin (24-fold) in mouse kidney homogenates at 7 d recovery after severe ischemia. We found sustained induction of Muc1/beta-catenin was associated with some epithelial-to-mesenchymal transition features: a significant 10-fold increase in vimentin and a significant 63% reduction of E-cadherin. We observed a significant 1.8-fold increase in levels of phosphorylated p53 that induces cell cycle arrest by upregulating p21 transcription, which mediates kidney fibrosis. As total p53 increased 1.2-fold after 7 d recovery, the increased ratio [active phosphorylated : total p53] was approaching significance.

Conclusion: Enhancing the Muc1/beta-catenin levels by selective genetic and chemical inhibition of GSK3? revealed a protective role for this axis in a HgCl2-induced model of AKI. An early and transient activation of the axis after AKI appears to be renoprotective by promoting repair, while sustained activation of the same axis promotes renal interstitial fibrosis and accelerates AKI to CKD progression. Thus, it seems that the Muc1/beta-catenin pathway acts as a “double-edge sword” in the injured kidney.
5-A Poster: PIF1 helicase ablation increases diet-induced weight gain and alters whole animal metabolism

Presenter: Frances Belmonte, Post-Doctoral Fellow
Research Interest: Bench Cardiology

Mentors: Brett Kaufman PhD
Funding Source: T32

Authors: Frances Belmonte PhD, Nikolaos Dedousis, Michael Jurczak PhD, Robert O’Doherty PhD, Brett Kaufman PhD

Introduction: The expression of RNA/DNA helicase Pif1 is downregulated in human skeletal muscles from obese insulin-sensitive, obese insulin-resistant, and obese type II-diabetic subjects compared with lean controls. We previously reported that mice lacking the Pif1 gain weight when fed a normal chow diet. We have ruled out a skeletal muscle defect (the primary consumer of glucose). To determine how PIF1 contributes to weight homeostasis, wild type (WT) control and Pif1 knockout (PIF1 KO) mice were fed a high fat diet and underwent whole animal metabolic phenotyping.

Methods: Age- and weight-matched male and female wild type controls and PIF1 KO mice were subjected to a high fat diet for 16 weeks. Total body weights and food intake were measured weekly. For three weeks during the study, food intake was measured several times per week for more robust food intake measurements. Animals at 3-months-of-age underwent whole body metabolic measurements. Blood glucose clearance, serum leptin levels, liver triglycerides, and liver histology were performed. Lean and fat tissue content were measured via body composition analyses using Echo magnetic resonance imaging.

Results: Unexpectedly, we found that PIF1 KO females gained more fat weight on a high fat diet when compared with WT female mice. Food intake was determined to be the primary driver of obesity in the PIF1 KO females. Notably, indirect calorimetry revealed that KO females have increased energy expenditure, which could be the driver of over-eating. Additionally, we observed that KO females have decreased ambulatory activity. Blood glucose clearance was unchanged in KO females while serum leptin was increased in KO females compared with female WT controls. Conversely, KO males fed a high fat diet are comparable in weight, feeding, and energy expenditure compared with control males, but also show decreased ambulatory activity, suggesting that weight gain in males is independent of decreased movement. Collectively, our results suggest a gender-specific role of Pif1 in satiety.

Conclusion: Our findings propose a novel role of Pif1 in maintaining weight homeostasis. Future studies will explore the gender-specific effects of a high fat diet in ovariectomized PIF1 KO female mice. These future studies will facilitate our understanding of how a RNA/DNA helicase such as Pif1 contributes to metabolism and health.
6-A Poster: KS-WNK1 is required for WNK Body Formation in Response to Potassium Stress

Presenter: Cary Boyd-Shiwarski, Post-Doctoral Fellow
Renal-Electrolyte

Research Interest: Bench

Mentors: Arohan Subramanya MD

Funding Source: T32

Authors: Cary Boyd-Shiwarski MD, Daniel Shiwarski PhD, Lubika Nkashama BS, Ankita Roy PhD, Brittany Rush BS, Rod Tan MD, Chou-Long Huang MD, Donna Stoltz PhD, Manoj Puthenveedu MD, Arohan Subramanya MD

Introduction: With-No-Lysine kinase 1 (WNK1) has 2 major isoforms that coordinate kidney NaCl and K+ transport: a ubiquitously expressed “Long” isoform (L-WNK1) with intact kinase activity, and a truncated kinase-defective “Kidney-Specific” (KS-WNK1) isoform that replaces the N-terminal kinase domain with 30 unique amino acids. In response to changes in dietary potassium, WNK signaling complexes concentrate in the distal convoluted tubule (DCT), forming large discrete punctate foci which we call “WNK bodies”. Though these structures have been observed by numerous investigators, their identity and the mechanisms that drive their assembly have remained obscure. Since KS-WNK1 is highly expressed in the DCT, we hypothesized that it is critical for WNK body formation.

Methods: The in vivo role of KS-WNK1 on WNK body formation was assessed using immunohistochemistry and immunofluorescence confocal microscopy in kidneys of control or KS-WNK1 KO mice treated with varying potassium diets. To identify sequences important for KS-WNK1 function, evolutionarily conserved residues in the unique KS-WNK1 N-terminus were modified by gBlock mutagenesis, and these cDNAs were expressed in cell models. In vitro WNK body formation was assessed by immunofluorescence, cell fractionation and palmitoylation assays, immuno-TEM, and live cell imaging.

Results: C-terminal antibodies recognizing both L- and KS-WNK1 identified punctate structures in the DCT of mice maintained on either low or high potassium diets; WNK bodies were absent in mice on control diets. Mice lacking KS-WNK1 were unable to form WNK bodies in the DCT in response to potassium loading or restriction, indicating that KS-WNK1 is essential for their formation. In our cell model, KS-WNK1 collected in similar puncta, whereas L-WNK1 was distributed diffusely throughout the cytoplasm. Both in vivo and in vitro models confirmed that WNK bodies are membraneless structures that contain WNK1, WNK4, and SPAK, and well as ribosomal protein L22. WNK bodies did not co-localize with lysosomes, endosomes, autophagosomes, stress granules, or lipid droplets. Live cell imaging and FRAP assays displayed dynamic punctate structures that restrict KS-WNK1 diffusion into the free cytosol. In cells, KS-WNK1 puncta formation was dependent on a palmitoylated cysteine-rich hydrophobic motif harbored in its unique N-terminus, as ablation of this motif shifted KS-WNK1 diffusely.

Conclusion: These findings indicate that WNK bodies are KS-WNK1-dependent membraneless structures that sequester the WNK signaling pathway in response to changes in dietary K+. Furthermore, our data suggest KS-WNK1’s unique N-terminus functions as a hydrophobic core for WNK body assembly. Our future studies aim to elucidate how these novel structures coordinate the renal response to potassium stress.
**Introduction:** Acute pulmonary thromboembolism (PTE) is a major vaso-occlusive pulmonary complication associated with high morbidity. Despite advances in diagnosis and treatment, the pathophysiology of PTE remains incompletely understood. Although entrapment of circulating platelet aggregates in the pulmonary arterioles is believed to promote PTE, in vivo evidence to support this mechanism does not exist.

**Methods:** ADP, collagen or thrombin were administered intravascularly (IV) to wild type (WT) mice and the pulmonary microcirculation was studied using multi-photon-excitation (MPE) enabled quantitative intravital fluorescence lung microscopy (qFILM). Fluorochrome-conjugated CD49b Ab and dextran was administered IV for in vivo staining of circulating platelets and visualization of blood vessels. Time series of qFILM images were collected at baseline and immediately following IV administration of ADP, collagen or thrombin. Image sequences were analyzed to identify PTE, which was defined as occlusion of blood vessels with platelet aggregates leading to stasis of blood flow.

**Results:** ADP (2.5-100 mg/kg), collagen (0.2-10 mg/kg) and thrombin (250-1000 U/kg) evoked dose-dependent PTE in mice. Large circulating platelet aggregates were observed to arrive in the pulmonary arterioles and occlude the arteriolar bottle-necks located between the pulmonary arterioles and capillaries. The occlusion of arteriolar bottle-necks led to stasis of blood flow in the arteriolar and the down-stream capillaries. Surprisingly, unlike collagen or thrombin, ADP induced PTE was not stable and resolved over a time period of 10 min. Thrombin (500 U/kg) and collagen (7.5 mg/kg) threshold doses evoked protracted responses with a stable emboli formation.

**Conclusion:** We introduce an intravital microscopy approach to probe agonist-dependent platelet aggregation in the lung of live mice. We provide the first real-time visual evidence showing that PTE involves entrapment of large circulating platelet aggregates in the pre-capillary pulmonary arterioles. Our model has potential uses in investigating the molecular determinants of platelet function and thrombosis within the pulmonary circulation as well as the pharmacology of antithrombotic compounds.
**11-A Poster:** Therapeutic targeting of ERK1/2-p90RSK-CDC25C signaling pathway overcomes acquired resistance to Ganetespib, an Hsp90 inhibitor, in KRAS mutant NSCLC.

**Presenter:** Suman Chatterjee, Post-Doctoral Fellow

**Hematology/Oncology**

**Research Interest:** Bench

**Mentors:** Timothy F. Burns MD

**Funding Source:** LUNGevity

**Authors:** Suman Chatterjee PhD, Eric H-B Huang MS, Ian Christie BS, Timothy F. Burns MD

**Introduction:** A subset of non-small cell lung cancers (NSCLC) are dependent upon oncogenic driver mutations including the most frequently observed driver mutant KRAS which is associated with a poor prognosis. As direct RAS targeting in the clinic has been unsuccessful to date, use of Heat shock protein 90 (Hsp90) inhibitors appeared to be a promising therapy for KRAS mutant NSCLC, however limited clinical efficacy was observed due to rapid resistance. Furthermore, the combination of the Hsp90 inhibitor (Hsp90i), ganetespib and docetaxel was tested in a phase III clinical trial and failed to demonstrate benefit. Here, we investigated the mechanism(s) of resistance to ganetespib and explored why the combination with docetaxel failed in the clinic.

**Methods:** Growth inhibitory effects of the drugs were determined through the colony formation and MTS assays. Ganetespib resistant (GR)-KRAS mutant NSCLC cell lines were derived to analyze resistance mechanism(s). Flow-cytometry was performed to assess cell-cycle profiles of parental and GR cells or cells with gene specific overexpression. Expression of proteins was examined by immunoblotting. Efficacy of novel Hsp90i combinations was tested in vivo using both NSCLC xenograft and patient-derived xenografts.

**Results:** We have not only identified the mechanism of ganetespib resistance (GR) but have also found that GR leads to cross-resistance to docetaxel. Reactivation of p90RSK and its downstream target, CDC25C was critical for ganetespib and docetaxel resistance, which was mediated via bypass of a G2/M arrest. Overexpression of either p90RSK or CDC25C proved sufficient to bypass the G2/M arrest as well induce resistance in vitro and in vivo. Moreover, the observed resistance was dependent on p90RSK/CDC25C signaling, as synthetic lethality to ERK1/2, p90RSK or CDC25C inhibitors was observed. Importantly, the combination of ganetespib with inhibitors of p90RSK or CDC25C was highly efficacious in parental cells and in vivo.

**Conclusion:** Despite two decades of testing in the clinic, Hsp90 inhibitors have been ineffective due to resistance. Our preclinical studies investigating the combination of ganetespib with inhibitors of ERK1/2, p90RSK or CDC25C demonstrated significant efficacy and provide a way forward for the rationally designed Hsp90 inhibitor combinations that will prevent and/or help overcome resistance.
**12-A Poster:** A gain-of-function variant at the extracellular domain core of the epithelial Na+ channel

**Presenter:** Jingxin Chen, Post-Doctoral Fellow  
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** Shaohu Sheng MD  
**Funding Source:** P30 DK079307

**Authors:** Jingxin Chen MD, Shaohu Sheng MD, Thomas Kleyman MD

**Introduction:** Epithelial Na+ channels (ENaC) play a critical role in the regulation of extracellular fluid volume and blood pressure. Recent human genome sequencing has revealed a large number of ENaC gene variants. However, the functional consequences of the vast majority of human ENaC variants are unknown. In this study, we investigated several non-synonymous ENaC variants located at a beta strand within a core beta-ball structure of the extracellular domain for their functional roles.

**Methods:** Point mutations corresponding to the selected variants were introduced into human alpha ENaC cDNA by site-directed mutagenesis. Wild type (WT) and mutant alpha subunits, together with WT beta and gamma subunits of human ENaCs were expressed in Xenopus oocytes by cRNA injections. Channel activities were examined by two-electrode voltage clamp. The determined amiloride-sensitive currents in cells expressing WT and mutant ENaCs were compared to assess the effects of the mutations on ENaC activity. Channel densities in oocyte plasma membranes were examined by a luminescence assay using a FLAG epitope tag inserted into the extracellular domain of beta subunit. Na+ self-inhibition was determined by measuring the decrease in current from the peak to the steady state elicited by a rapid increase in extracellular Na+ concentration from 1 to 110 mM at a holding potential of -100 mV.

**Results:** The structure of the ENaC-homologous acid sensing ion channel 1 (ASIC1) shows six residues within beta 7 strand, one of the five beta-ball strands within the extracellular domain core. Four out of the six human alpha ENaC residues within its homologous beta 7 strand has at least one identified variant. We first examined three variants within the region. Oocytes expressing the R350W ENaCs showed two-fold greater amiloride-sensitive currents than cells expressing WT channels (p < 0.001, Student t test, n=39). The variation did not significantly alter channel surface expression (p > 0.05, n= 19~21). The mutant channels showed a diminished Na+ self-inhibition, which correlates to an increased open probability. The V351A mutant had a reduced currents (55% of WT channels, p < 0.001, n=34 or 35), whereas G355R showed an increased current (1.6-fold of WT, p = 0.001, n=35 or 36).

**Conclusion:** Our study identified two novel gain-of-function human ENaC variants, R350W and G355R, and one loss-of-function variant, V351A. The relatively large effect of R350W is likely due to an altered channel gating. Its location within a well-conserved core beta strand at a subunit interface and the existence of nearby functional variants suggests that its residing beta strand has an important role in ENaC gating regulation.
13-A Poster: A mouse model of intra-abdominal candidiasis following intraperitoneal inoculation of C. glabrata and Zymosan mimics disease in humans, and generates more reproducible data than a C. glabrata-sterile stool model

Presenter: Shaoji Cheng, Junior Faculty Research Interest: Bench Infectious Diseases

Mentors: None Funding Source: None

Authors: Shaoji Cheng MD, Binghua Hao MD, Cornelius J Clancy MD, M Hong Nguyen MD

Introduction: C. glabrata does not consistently kill mice after intravenous (IV) infection in the absence of severe immunosuppression or extremely high inocula. We developed a model of intra-abdominal candidiasis (IAC), in which mice are infected by an intra-peritoneal (IP) inoculation of C. glabrata mixed with sterile stool. The model discriminates the relative virulence of clinical strains and results in peritonitis and intra-abdominal abscesses similar to human IAC. However, the complex composition and batch-to-batch variation of sterile stool may limit standardization. We explored alternative adjuvants to sterile stool.

Methods: We infected immunocompetent male ICR cd1 mice IP with C. glabrata admixed with lipopolysaccharide (LPS) or Zymosan A.

Results: No mice died over 14 days following IP challenge with 5x10^8 CFU of C. glabrata BG2 alone, 5-20 mg/kg of Zymosan alone, or 7.5 mg/kg of LPS alone. The mortality rate was 37.5% following IP challenge with 15 mg/kg of Zymosan alone. Mortality rates among mice infected with 5x10^8 CFU of BG2 + 5, 10 or 20 mg/kg of Zymosan were 60, 75 and 100%, respectively. Mice began to die on day 2, and no mice died after day 4. There was no mortality among mice infected with 5x10^8 CFU of BG2 + 7.5mg/kg of LPS. Mice infected with 5x10^8 BG2 +15 mg/kg of LPS began to die on day 2, and the mortality rate was 100% on day 3. Burdens of C. glabrata within parenchyma of liver, spleen and pancreas at times of sacrifice were >8-log10 CFU/g tissue, suggesting that mice died from overwhelming Candida sepsis. IAC following sublethal IP inoculation of BG2 and Zymosan resulted in brisk neutrophil infiltration into the peritoneal cavity, and recapitulated the progression of disease in humans from peritonitis to intra-abdominal abscesses. There were no deaths among mice infected IV with 5x10^8 BG2 + IP challenge with 20mg/kg of Zymosan or 7.5 mg/kg of LPS.

Conclusion: An immunocompetent mouse model of IAC in which C. glabrata and Zymosan are co-inoculated IP mimics IAC in humans, and generates more reproducible data than are obtained following IP inoculation of C. glabrata and sterile stool. The C. glabrata-Zymosan model reliably causes mortality in a Zymosan dose-dependent manner. Mortality rates, tissue burdens and pathology observed over a range of C. glabrata inocula suggest that the model will be suitable for comparative virulence studies, and for transcriptome profiling by RNA-Seq.
**14-A Poster:** Myeloid cells involvement in hindlimb ischmia induced Atherosclerosis

**Presenter:** Emilie Coppin, Post-Doctoral Fellow  
**Research Interest:** Bench Vascular Medicine Institute

**Mentors:** Partha Dutta PhD  
**Funding Source:** None

**Authors:** Emilie Coppin PhD, Jonathan Florentin PhD, Sathish Babu Vasamsetti PhD, Partha Dutta PhD

**Introduction:** Patients with peripheral artery disease (PAD) die due to cardiovascular abnormalities, primarily myocardial infarction, which is a complication of atherosclerosis. In a mouse model of hindlimb ischemia (HI), we found increased production of inflammatory myeloid cells, which causes increased inflammation in atherosclerotic plaques. However, it is not known how these inflammatory myeloid cells are produced after HI.

**Methods:** We induced HI in C57BL/6 wild type mice, and ApoE Knockout mice fed on high fat diet (42 % of fat), which is a well know model for atherosclerosis. We analyzed myeloid cells populations and Hematopoietic Stem and Progenitors cells (HSPC) 2, 5, 7 and 21 days after HI.

**Results:** Our preliminary results showed that HI increased the number of myeloid cells (CD11b+), particularly neutrophils (Ly6G+) and Ly6Chigh monocytes in the blood and aorta of ApoE-/- mice. We found that HI drove HSPC and granulocyte macrophage progenitor cells (GMP) into the cell proliferation cycle. Furthermore, HSC sorted from the bone marrow of mice after HI expressed high levels of PU.1, a myeloid transcription factor, indicating myeloid bias of HSC after HI.

**Conclusion:** These data suggest that hindlimb ischemia increases differentiation of hematopoietic progenitors into myeloid cells, which infiltrate atherosclerotic plaques and make the plaque vulnerable to rupture.
Introduction: Bladder umbrella cells, which line the mucosal surface of the urothelium, undergo regulated exocytosis of subapical discoidal/fusiform-shaped vesicles (DFVs) in response to bladder filling. These urothelial responses allow the bladder to accommodate increasing urine volumes, to preserve its barrier function, and to communicate the filling state of the bladder to the CNS. Despite their physiological importance, we have limited insights into how these mechanically triggered trafficking events are regulated at the molecular level. RAB GTPases are known to play crucial roles in promoting vesicle movement, fusion and fission and work to date implicates the action of a RAB11A-RAB8A-MYO5B module in umbrella cell exocytosis. However, this protein complex may account only partially for the whole exocytic phenomena and there may well be other members of the RAB GTPases involved. It was previously shown that RAB27B is also localized to DFVs and knockout mice lacking RAB27B expression are reported to have reduced numbers of DFVs. Thus, we sought to determine whether RAB27B regulates DFV exocytosis and to establish its relationship with the RAB11A-RAB8A-MYO5B module.

Methods: RABs expression and localization in the rat bladders were assessed by immunofluorescence and colocalization was measured using the Squash protocol. Exocytosis was determined by measuring the release of hGH from umbrella cells of rat bladders transduced with adenoviruses encoding for hGH1-V5.

Results: Here we show that in native rat urothelium RAB27B is found in DFVs that extend past a KRT20 subapical network, and accumulate close to the apical surface of the umbrella cells. We observe that RAB27B-positive DFVs exhibit the highest degree of colocalization with RAB27A (~40%) and RAB3A (~30%), and less colocalization with RAB11A (~20%) and RAB8A (~20%). If the RAB11A-RAB8A-MYO5B module acts upstream of RAB27B, as has been recently proposed, then disruption of the former should impair formation of RAB27B DFVs. However, upon expression of dominant-active or dominant-negative mutants of RAB11A or RAB8A, we do not observe a significant effect on the size, number, or intensity of RAB27B-positive DFVs. Likewise, reduction of RAB27B expression by transduction of the urothelium with an adenovirus encoding a RAB27B-specific shRNA has no effect on RAB11A-positive DFVs. We observe that filling-induced exocytosis of hGHV5-loaded DFVs in an ex vivo bladder preparation is significantly inhibited by 42 ± 16% when RAB27B expression is down regulated.

Conclusion: Our data indicate that RAB27B regulates DFV exocytosis, but in a manner that may be independent of the previously described RAB11A-RAB8A-MYO5B module.
16-A Poster: Hepatic insulin sensitivity is improved in high-fat diet (HFD) fed PARKIN KO mice in association with increased hepatic AMPK activation and reduced steatosis.

Presenter: Lia Edmunds, Post-Doctoral Fellow  
Research Interest: Bench Endocrinology and Metabolism

Mentors: Michael Jurczak PhD  
Funding Source: T32

Authors: Lia R. Edmunds PhD, Brydie R. Huckestein BS, Yanxia Chu BS, Yingze Zhang PhD, Michael J. Jurczak PhD

Introduction: PARKIN is a ubiquitin E3 ligase that plays a critical role in a mitochondrial quality control process called mitophagy. During mitophagy, damaged mitochondria are selectively degraded following ubiquitination of outer mitochondrial membrane proteins by PARKIN. We recently demonstrated PARKIN knockout (KO) mice are protected from diet-induced obesity due in part to altered intestinal lipid absorption. Furthermore, hepatic insulin sensitivity was improved in high-fat diet (HFD)-fed PARKIN KO mice, independent of changes in body weight.

Methods: Six-week old male WT and PARKIN KO mice were fed a control low-fat diet (LFD; 10% kcal fat) for six weeks and randomly assigned to either LFD or 10 day HFD (60% kcal fat) groups. To better understand the underlying mechanism(s) for the improved hepatic insulin sensitivity in PARKIN KO mice after 10 days HFD feeding, we evaluated key pathways commonly implicated in the pathogenesis of insulin resistance (IR) including changes in hepatic lipid metabolites, activation of the ER stress response and alterations in inflammatory cytokine levels and signaling.

Results: Liver triglycerides (TG) increased 40% in WT mice following HFD (p<0.05) while KO liver TG remained unchanged and was 36% less than HFD WT (p<0.05). Diacylglycerol levels, which positively associate with insulin resistance, were 60% less in KO mice (p<0.01) and ceramides were modestly elevated 13% (p<0.05). Transcriptional markers of the IRE1?, eIF2α, and ATF6 arms of the ER stress response were unchanged (Sil1, Atf4, Gadd34) or suppressed (Dnajb9, Edem, Rpn1, Dnajc3, Erp72, Ero1β; p<0.01) in HFD KO liver. Plasma cytokine levels were quite low, but TNFa, IL6 and IL10 were significantly increased in HFD KO mice. Plasma leptin was 17.8x less in HFD KO compared with WT (p<0.001) and resistin was modestly reduced (1.4x; p<0.08). Hepatic AMP:ATP was increased 1.8x(p<0.05) in HFD KO versus WT mice and was associated with increased phosphorylation of AMPK?(Thr172) (2.2x; p<0.01). Consistent with AMPK activation, malonyl-CoA was reduced 30% (p<0.05) and expression of several genes (Fasn, Hnf1a, Srebp1, A pob, Apoc3, Pklr) were significantly reduced.

Conclusion: Alterations in intestinal lipid absorption in PARKIN KO mice during HFD-feeding are associated with reduced hepatic energy charge, activation of AMPK and reduced liver triglyceride and diacylglycerol levels, in addition to reduced expression of ER stress response genes and increased plasma IL6, IL10 and TNFa levels. These data add to a growing body of evidence that suggests negative energy balance produces insulin sensitizing effects in liver through multiple mechanisms and further highlight the need for conditional PARKIN KO mice to understand the tissue-specific role of PARKIN.
17-A Poster: G-quadruplexes in mitochondrial function and human disorders

Presenter: Micol Falabella, Post-Doctoral Fellow  
Research Interest: Bench  
Vascular Medicine Institute

Mentors: Brett Kaufman PhD  
Funding Source: NIH

Authors: M. Falabella PhD, J. E. Kolesar PhD, Y. V. Taguchi MS, C. Wang PhD, M. Xiang PhD, J. Turek-Herman MS, S. P. Barrett MS, C. M. St. Croix PhD, N. Sondheimer MD, L. A. Yatsunik PhD, F. B. Johnson PhD, B. A. Kaufman PhD

Introduction: Mitochondrial disorders usually manifest as neuromuscular or hepatocerebral diseases, characterized by defects in the oxidative phosphorylation (OXPHOS) activity. Mitochondrial genome (mtDNA) stability and efficient gene expression are required for mitochondrial respiratory activity; however, the origin of defects in these processes is not always well understood. The mitochondrial genome is characterized by an asymmetric base composition with an enrichment of guanines (G) in the heavy strand. Single-stranded G-rich DNA or RNA sequences can adopt non-canonical structures known as G-quadruplexes (G4), hence mtDNA may be more prone to G4 formation, genome instability and gene expression defects. Our previous in vitro study showed that mtDNA can form G4 structures and demonstrated a strong correlation between G4 motifs and mtDNA deletion breakpoints, a form of genome instability. Here we report G4 structure formation, mediated by small molecule, causing mtDNA instability and aberrant gene expression, with magnified effects in the Leigh syndrome, a progressive infantile neurodegenerative disorder.

Methods: The mtDNA relative abundance was measured by a qPCR. RHPS4 mitochondrial localization was acquired in live HeLa cells labelled with MitoTracker Deep Red. Expression levels of mitochondrial protein were measured by immunoblotting. Gene expression was quantified by qPCR and RNA-seq. Oxygen Consumption Rate (OCR) of control and patient fibroblasts was measured using the XF-24 Seahorse system.

Results: To study the biological role of G4 structures in mitochondria we screened several G4 ligands for mtDNA alterations, identifying RHPS4 as the best candidate. RHPS4 is an acridinium salt that localizes to mitochondria and induces dose-dependent mtDNA depletion with hallmarks of replication pausing, which demonstrates a role for G4 in the mtDNA instability. Additionally, we observed that before mtDNA depletion occurs, the G4 stabilization impairs mitochondrial transcription and OXPHOS subunits expression. Biochemical analysis showed that RHPS4 is bona fide G4 compound able to stabilize antiparallel structures in mtDNA sequences. The RHPS4 effect was also studied on patient fibroblasts harboring the Leigh’s mutation T10191C, a mitochondrial mutation that increases the G4 formation potential. Respiratory measurement revealed that G4 stabilization in the patient cells induces severe oxygen consumption defects.

Conclusion: Our unprecedented observations suggest that G4 motifs may play a role in driving mtDNA instability and gene expression defects, particularly in presence of mitochondrial mutations that enhance the G4 potential formation.
**18-A Poster:** The Dexamethasone Transcriptomes in Cortical and Hypothalamic Embryonic Neural Progenitor Stem Cells

**Presenters:** Krystle Frahm, Post-Doctoral Fellow  
**Research Interest:** Bench Endocrinology and Metabolism

**Mentors:** Donald B. DeFranco PhD  
**Funding Source:** T32

**Authors:** Krystle Frahm PhD, Jacob Waldman BS, Uma Chandran PhD, Donald DeFranco PhD

**Introduction:** Fetal exposure to synthetic glucocorticoids reprograms distinct neural circuits in the developing brain, often in a sex-specific via mechanisms that remain poorly understood. In order to reveal whether such reprogramming is associated with select molecular signatures, we characterized the transcriptome of primary embryonic mouse cerebral cortical and hypothalamic neural progenitor stem cells (NPSCs) derived from male and female embryos exposed to the synthetic glucocorticoid, dexamethasone.

**Methods:** Global gene expression data sets were generated by RNA-Sequencing (RNA-Seq) analysis. Bioinformatic analysis of coding and noncoding genes identified differential expression of common and unique genes for region, sex, and/or glucocorticoid exposure.

**Results:** Bioinformatic analysis of coding and noncoding genes identified differential expression of common and unique genes for region, sex, and/or glucocorticoid exposure.

**Conclusion:** These gene expression datasets provide a unique resource that will inform future studies directed towards understanding the molecular mechanisms responsible for region- and sex-specific reprogramming of the fetal brain brought about by in utero exposure to excess glucocorticoids.
19-A Poster: Heme Promotes Pulmonary Hypertension in SCD by Inducing Secretion of Placenta Growth Factor From Erythroblasts via Oxidant Response Transcription Factors

Presenter: Oluwabukola Gbotosho, Post-Doctoral Fellow Research Interest: Bench Hematology/Oncology

Mentors: Gregory Kato MD, Maria Kapetanaki PhD Funding Source: HLBVascular Medicine Institute, Div. of Hem-Onc.

Authors: Oluwabukola Gbotosho PhD, Maria Kapetanaki PhD, Valerie Schrott BSc, Frances Weidart MSc, Solomon Ofori-Acquah PhD, Grant Bullock MD, Gregory Kato MD

Introduction: Patients with sickle cell disease (SCD) have elevated plasma levels of placenta growth factor (PlGF), which promotes expression of the pulmonary vasoconstrictor endothelin-1 (ET-1) contributing to pulmonary hypertension, an important age-related and life-limiting complication of SCD. In SCD patients, markers of high iron burden are associated with the highest PlGF levels, leading us to hypothesize a mechanistic link between excessive iron and the induction of the PlGF protein.

Methods: We have established in vitro models of heme-bound iron (hemin) stimulation of the PlGF promoter in human K562 cells and in murine primary erythrocyte cells. With the use of real time PCR we have assessed the transcriptional expression of PlGF and HO-1 as a result of that stimulation. Furthermore, we have established an in vivo murine model of PlGF response to heme exposure.

Results: Gene expression knockdown and small molecule inhibitor and activator experiments demonstrate a central role of NRF2 in activating the PlGF promoter in response to heme, supported by chromatin immunoprecipitation experiments. Intravenous injection of heme in wild type mice induces PlGF mRNA expression in bone marrow, and secretion of PlGF protein into blood within three hours. This response is dramatically blunted in mice deficient in NRF2, further supporting the importance of NRF2 in heme induction of PlGF expression in vivo.

Conclusion: Our results to date support a mechanism in which accelerated heme turnover in SCD promotes robust expression of PlGF in erythroblasts during erythroid differentiation, through a pathway that involves EKLF, NRF2 and MafG. This mechanism helps to explain the clinical observation that heavily transfused, iron overloaded adults with SCD are more likely to develop pulmonary hypertension, as a potential consequence of excess heme trafficking from the turnover of transfused red cells. These results might inspire greater adherence to existing approved therapies to chelate iron in SCD.
Introduction: Ultrasound-stimulated microbubbles are emerging as novel target-specific non-viral gene delivery vectors for the treatment of disease for which gene targets have been identified. The nature of the microbubble-target cell interactions that facilitate nucleic acid delivery across cell membranes and into cells outside the vasculature, and hence strategies to optimize the efficiency of this platform, remain poorly understood. The objective of this work is to link bubble cavitation with cellular permeability and membrane repair response.

Methods: Propidium iodide (PI) was diluted into the media as a marker for sonoporation. For a subset of microbubble-cell pairs (n=351), a simultaneous ultrafast bright-field (16 Mfps; UPMC-Cam) and standard epi-fluorescence (15 fps) imaging system was employed to couple microbubble physics (~µs) with membrane permeability dynamics (~ms). Microbubble-cell pairs were exposed to an ultrasound pulse (0.5-2MHz), with a pulse duration of 4-16 µs and pressures between 0.1-0.8 MPa. We next examined the resulting effects on cellular biophysics (~seconds to minutes) via live-cell confocal microscopy during sonoporation with visualization of the plasma membrane and Ca2+ signaling (n=12), both known factors involved in cell wound/poration repair.

Results: Maximum absolute microbubble expansion and associated shear stress were strong threshold indicators of sonoporation. For an 8 µs pulse, the oscillation (shear stress) threshold above which HUVECs perforate was 3.9, 2.6, and 1.4 µm (7.8, 14.5, 22.7 kPa) at 0.5, 1 and 2 MHz respectively. At a given frequency, increases in pulse duration decreased the required excursion and shear stress. Confocal microscopy highlights that microbubbles exposed to an 8 µs pulse generate heterogeneous pore patterns that reseal out-of-plane. Sonoporation also affects intercellular Ca2+ concentrations in both sonoporated and adjacent, non-sonoporated cells. Maximum relative Ca2+ concentrations in non-sonoporated cells was found to decrease with increasing pore proximity (p<0.003).

Conclusion: Large-magnitude (~kPa), short-duration (~µs) shear stresses generated by ultrasound-stimulated microbubbles in proximity to HUVECs induces sonoporation in a threshold-dependent manner, requiring larger shear magnitudes with increasing frequency and decreasing duration. Once achieved, sonoporation induces membrane perforations that repair via apical-to-basal membrane resealing, occurring over minutes. Further, sonoporation affects Ca2+ signaling in both treated and neighboring cells, suggesting its role as an important secondary messenger in the remote effects of intravascular sonoporation. This contributes towards the substantiation of the merit of sonoporation as a non-viral delivery platform by linking the salient ultrasound-triggered cavitation physics with the resulting effects on cellular function.
Introduction: Calcific aortic valve disease (CAVD) is present in ~2% of individuals over 60 years of age. The most common risk factors for the development of CAVD are hypertension, hypercholesterolemia, diabetes, and aging. Senescence is a proliferative control mechanism whereby different factors such as telomere shortening, DNA damage, and chromatin acetylation or methylation, limit cellular proliferation. It is well established that macrophages drive the inflammatory process in atherosclerosis, and telomerase (TERT) was found to be active in macrophages localized to human atherosclerotic plaques, suggesting that attenuating TERT activity may be protective. The objective of this study is to evaluate the different roles of TERT in CAVD.

Methods: Von Kossa staining was used to categorize healthy and calcified valves from human donors into calcified and healthy. Immunohistochemistry was used to identify the presence and localization of TERT, p53, PCNA and H2AX in the tissues. Valve interstitial cells (VICs) from the same donors were cultured under osteogenic conditions and the expression of TERT and H2AX was assessed. RNA expression of proliferation and senescence-associated markers will be quantified by qPCR. Mechanistic studies on how TERT participates in the calcification process will be performed by modulating TERT expression and activity in VSMC and VICs using genetic and chemical tools, such as knock-out, knock-down and drugs like GRN163L or Saquinavir, to block or enhance TERT mRNA expression.

Results: In all cases, there was not co-localization of the proteins of interest with von Willebrand factor (endothelial marker). TERT, PCNA and p53 appeared increased in calcified valves compared to control valves. No cellular death was detected in the VICs studies. The calcium staining and posterior quantification showed a higher predisposition of cells from CAVD valves to calcify compared to those from healthy controls. The expression of TERT was clearly superior in the VICs from the CAVD valve, corroborating the results obtained in the complete valve tissue. H2AX expression showed contradictory results.

Conclusion: TERT is increased in human calcified aortic valves as well as in VICs isolated from the same valves under osteogenic conditions, also PCNA and p53 are both increased in the calcified valves. TERT and PCNA are associated with cell proliferation, but p53 stops it, keeping open different hypothesis about their role (chromatin modification, signaling or most likely proliferation regulation) in CAVC. VICs from calcified valves are more prone to calcify under osteogenic conditions in vitro than controls indicating changes not only in the calcified cells, but also in the peri-calcificed areas.
Introduction: There is an increased prevalence of underactive bladder (UAB) symptoms in the aging population, which is characterized by incomplete bladder emptying associated with a decline in detrusor contractility, urethral pressure, and bladder sensation. The pathogenic mechanisms remain unclear, and there are currently no reliable therapeutic options to treat or cure UAB. However, aging also correlates with an overall increase in fibrosis throughout the body, including the bladder, where it leads to decreased compliance and force generation and thus may be a contributing factor to UAB. We used 24-month-old male and female rats, and 9-month-old controls, to assess the effects of age-related bladder fibrosis on contractile function and histological changes and the therapeutic benefits of the antifibrotic hormone, relaxin, currently in phase 3 clinical trials for treating acute decompensated heart failure.

Methods: Aged (24 month) and adult (9 month) male and female F344 rats were administered recombinant human relaxin-2 (400 µg/kg/day) or saline for 14-days via subcutaneous ALZET osmotic pumps. At the end of the treatment period, bladder sheet contractile function was assessed in vitro using length-tension measurements and responses to agonists and electrical field stimulation. Bladder wall morphology was examined in histological sections stained for collagen and elastin deposition.

Results: Length-tension studies demonstrated that aged male rats had significantly increased passive tension compared to younger males, suggesting there is decreased bladder elasticity and compliance with aging. However, decreased compliance was not observed in aged females. Relaxin treatment of aged males showed a return of passive tension profiles comparable to adults. Histological data were correlated with functional studies, where aged males showed increased bladder collagen content that decreased following relaxin treatment. Relaxin also increased expression of L-type Ca2+ channels (CaV1.2) in the detrusor layer, which can contribute to increased force generation.

Conclusion: These data demonstrate a sex-specific consequence of aging, where male rats are more prone to develop bladder fibrosis than females. However, in female rodents, endogenous relaxin plasma levels were found to be twice as high as that in males (250 ± 50 pg/ml versus 115 ± 31 pg/ml, respectively) which may be protective against developing bladder fibrosis. In aged female rats, overactive bladder symptoms (OAB) were observed that may progress to UAB with time. Importantly, we demonstrated the therapeutic benefits of relaxin in reversing fibrosis and increasing the contractile properties of the detrusor, which represents a new therapeutic option for treating/curing fibrosis-related UAB.
**Introduction:** Chronic kidney disease (CKD) is increasingly recognized as a major public health problem, and has a prevalence of 10% in the general population. Death due to cardiovascular disease and infection is a major clinical problem in patients with kidney diseases. Uremia as a cause of kidney dysfunction results in impaired immune response and microbial infection, and sepsis account for 20% of deaths in ESRD patients. The intestinal dysbiosis and change in gut permeability are noted in uremic patients. However, the cellular and molecular mechanisms involved in intestinal dysbiosis in uremic condition is poorly understood.

**Methods:** To investigate the role of uremia in intestinal dysbiosis, we used the mouse model of Aristolochic acid nephropathy (AAN) in C57BL6 male mice. Mice were injected intraperitoneally (ip) with 10 mg/kg body weight aristolochic acid I (AAI). For pharmacological inhibition study, mice were ip injected with probenecid 150mg/kg, 30 min before the administration of AAI. Intestinal lamina propria cells populations were determined by flow cytometry. The gut permeability to 4-kDa FITC-dextran was determined, and bacterial translocation was assessed by plating the tissue homogenates on brain heart infusion (BHI) agar.

**Results:** A single intraperitoneal injection of aristolochic acid I (AAI) resulted in severe tubulointerstitial injuries accompanied by increased level blood urea nitrogen (BUN). Mice with kidney dysfunction showed increased intestinal permeability, translocation of living bacteria across the intestinal barrier and an increased number of activated T lymphocytes in spleen and mesenteric lymph nodes. Flow cytometry analysis of small intestine (SI) lamina propria cells revealed the significant reduction in neutrophils and T helper 17 cells in mice with kidney dysfunction. Treatment with probenecid prevented kidney dysfunction and consequently inhibited change in intestinal permeability and bacterial translocation.

**Conclusion:** These results indicate that uremia associated with kidney dysfunction accounts for increase in intestinal permeability, gut microbiota dysbiosis and translocation in internal organs.
26-A Poster: Exercise protects against hypoxia-induced pulmonary vascular remodeling in mice.

Presenter: Neil Kelly, Post-Doctoral Fellow Cardiology

Research Interest: Bench

Mentors: Stephen Chan MD, Imad Al Ghouleh PHD

Funding Source: Medical Scientist Training Program

Authors: Neil Kelly MD, Leonard Estephan, Miranda Tai MS, Christopher Lee BS, Jingsi Zhao MS, Ying Tang BS, Anna Ramos BS, Imad Al Ghouleh PhD, Stephen Chan MD

Introduction: The risks and benefits of exercise remain controversial in clinical pulmonary hypertension (PH). While the value of exercise in overall health is widely appreciated, its associated increase in cardiac output in the setting of right ventricular dysfunction and poor pulmonary vascular compliance has led some physicians to caution against the utility of exercise in PH patients. In this study, we sought to determine the effects of exercise on pulmonary vascular disease progression in a preclinical model of group 3 PH.

Methods: Male C57BL/6J male mice were housed in cages exposed to room air (normoxia; 20% O2) or hypoxia (10% O2) for 4 weeks with either no, low-speed (0.5km/hr), or high-speed (1km/hr) treadmill exercise for 1 hour daily, 5 days per week. Statistical comparisons were made by two-way (RVSP, miRNA expression) or one-way (vascular remodeling) ANOVA.

Results: Terminal right ventricular (RV) catheterization demonstrated a significant decrease in RV systolic pressure (RVSP) in high-speed hypoxic exercise groups compared to unexercised controls (P < 0.005). Quantification of medial thickness in small (20-60 micron diameter) pulmonary arterioles revealed significant decreases in the medial indices (P < 0.05) and percent medial areas (P < 0.05) of hypoxic high- and low-speed exercised mice versus hypoxic unexercised controls. A screen of microRNA expression in total lung homogenate from these mice showed significant and dose-dependent upregulation of miR-134 with high-speed exercise in the setting of hypoxia. Putative targets of miR-134 obtained from public databases (TargetScan and DIANA-microT-CDS) were functionally classified by gene set enrichment analysis which revealed enrichment of genes involved in the DNA damage response (DDR). Western blotting of lung homogenate suggested a dose-dependent increase in gammaH2AX, a marker of DDR, with increasing treadmill exercise speeds.

Conclusion: These results show that exercise protects against elevated RVSP and pulmonary vascular remodeling in hypoxic mice. Our preliminary data suggest that miR-134 may contribute mechanistically to this phenotype by activating the DDR, which is known reduce the rate of cellular proliferation and, hence, may temper vascular remodeling in the setting of chronic hypoxia. Further in vitro characterization is underway to elucidate the combinatorial effects of miR-134 and hypoxia on proliferative phenotypes and cellular signaling pathways in pulmonary arterial endothelial and smooth muscle cells.
Introduction: Twist1 is a member of the basic helix-loop-helix family of transcription factors with multiple functions. It is an inhibitor of NF-κB signaling and plays a role in mediating the pathologic pro-survival phenotype of fibroblasts. CXCL12 is regulated by non-canonical NF-κB signaling (p52/RelB) and exerts its profibrotic effects through recruitment of T-cells and matrix-producing cells including bone marrow-derived cells known as fibrocytes. Following silencing of twist1 in lung fibroblasts, we have found increased expression of CXCL12 and RelB. We hypothesized that Twist1 directly binds to and regulates CXCL12 and RelB.

Methods: Twist1 binding site, E-Box motifs, CANNTG, were identified by sequence scanning for the 2 kb upstream sequences from the transcription start site (TSS) of human CXCL12 and RelB gene using Sequencher 5.0 (Genecode). Twist1 specific chromatin immunoprecipitation (ChIP) assay was performed using A549, MRC5 and human primary lung fibroblasts. DNA sequences containing putative E-box binding motifs were amplified by PCR using DNA from the ChIP assay.

Results: A total of 5 and 12 E-Box binding motifs were identified for CXCL12 and RelB, respectively. The E-Box binding motif located at -1046 bp from TSS of the CXCL12 gene was positive for Twist1 binding in A549, MRC-5 cells. We tested a total of three independent fibroblast lines from donor and IPF lungs and two of the three fibroblasts of both donor and IPF lungs were positive for Twist1 binding at this site. Among the 12 identified E-Box binding motifs for RelB gene, the E-Box binding motifs at -1318 bp and -1389 bp from TSS are potentially functional as Twist1 binding was detected in A549, MRC5 and two of the control lung fibroblasts in the DNA sequences containing both motifs. However, no binding was detected in this region in any of the three IPF lung fibroblasts. Because of the proximity of these two E-Box binding motifs, a common PCR reaction was designed to cover both sites. Therefore, one or both of these motifs may support Twist1 binding.

Conclusion: We have identified a functional Twist1 binding site in the CXCL12 promoter and two potential functional sites in the RelB promoter. These results support that Twist1 interacts with E-box binding motifs in the 5'UTRs of CXCL12 and RelB. Therefore, Twist1 may exert its role in IPF, in part, by regulating RelB and CXCL12 gene expression.
28-A Poster: Comparison of traditional and albumin-binding Lu-177-labeled phosphoramidate-based PSMA inhibitors for targeted radionuclide therapy of prostate cancer

Presenter: Xiaoxi Ling, Post-Doctoral Fellow  
Cardiology  
Research Interest: Bench

Mentors: Carolyn Anderson PhD  
Funding Source: NIH SBIR

Authors: Xiaoxi Ling PhD, Jonathan Geruntho PhD, Cindy Choy PhD, Joseph Latoche BS, Sophia Beyer BS, Beatrice Langton-Webster PhD, Carolyn Anderson PhD, Clifford Berkman PhD

Introduction: Prostate-specific membrane antigen (PSMA) has been described as an 'ideal biomarker' because of its restricted expression on prostate cancer cells and is increased on late-stage, androgen-independent, and metastatic prostate tumors. Consequently, PSMA remains an active target for the delivery of imaging and therapeutic agents. One of the challenges for small-molecule PSMA inhibitors with respect to delivering therapeutic payloads is their rapid renal clearance.

Methods: In order to overcome this pharmacokinetic challenge, we outfitted a 177Lu-labeled phosphoramidate-based PSMA inhibitor (CTT1298) with an albumin-binding motif (CTT1403) and compared its in vivo performance with that of an analogous compound lacking the albumin-binding motif (CTT1401). A direct comparison in vitro and in vivo performance was made for CTT1401 and CTT1403; the specificity and efficacy by means of PC3-PIP cellular uptake and internalization. Biodistribution, and therapeutic efficacy in PC3-PIP and PC3 (PSMA negative) tumor-bearing mice were determined for both compounds.

Results: Both compounds displayed excellent uptake and rapid internalization in PC3-PIP cells. In vivo, the albumin binding moiety in CTT1403 conferred clear advantages to the PSMA inhibitor scaffold including greatly enhanced circulating half-life and prostate tumor uptake that continued to increase up to 48-72 h post-injection (up to 50% ID/g in the tumor). Importantly, the tumor:kidney ratio of CTT1403 was 0.8 to 1.2 over all time points. This increased tumor uptake translated into superior therapeutic efficacy of CTT1403 in PSMA+ PC3-PIP human xenograft tumor. Five out of eight animals received CTT1403 treatment managed to survive over 200 days.

Conclusion: By introducing an albumin-binding motif to a small-molecule PSMA inhibitor scaffold, we significantly extended its circulating half-life and enhanced its tumor uptake without compromising its cellular uptake and internalization, thereby overcoming the challenges of rapid renal clearance for small-molecule PSMA inhibitors. Further, CTT1403 showed impressive therapeutic efficacy (>60% survival out to 200 days) in tumor-bearing mice.
29-A Poster: Ubiquitination of the interferon gamma receptor alters interferon gamma signaling

Presenter: James Londino, Post-Doctoral Fellow
Research Interest: Bench Pulmonary, Allergy and Critical Care Medicine

Mentors: Rama Mallampalli MD
Funding Source: AHA Postdoctoral Grant

Authors: James Londino PhD, Dexter Gulick BS, Travis Lear BS, Tomeka Suber MD, Nathaniel Weathington MD, Bill Hen PhD, Rama Mallampalli MD

Introduction: Interferon gamma signaling plays an important role in the resolution of bacterial and viral infection by enhancing antigen presentation, increasing expression of inducible nitric oxide synthase (iNOS), and the enhancement of NADPH oxidase components and the respiratory burst. Interferon gamma receptor 1 (IFNGR1) binds IFN gamma and complexes with IFNGR2 to initiate signaling. Although alteration of IFNGR1 expression has been shown to modify IFN gamma signaling, little is known about how the receptor's stability is regulated.

Methods: THP-1 monocytes were differentiated into macrophages with 20ng/mL PMA for 24h prior to experiments. IFNGR1-V5 was cloned into a pWPI vector in order to generate lentivirus for THP-1 experiments. HEK cells with recombinant cas9, crRNA and tracr RNA targeted against the IFNGR1 receptor gene locus from IDT oligonucleotides. Cells were co-transfected with homology directed repair (HDR) plasmids from Santa Cruz, selected with puromycin, and grown-up from single colonies to obtain knockout cells.

Results: We examined the half-life of IFNGR1 in epithelial and monocytic cell lines via cycloheximide chase experiments and determined that the half-life of the receptor was significantly extending by inhibiting proteasomal degradation. By overexpressing and immunoprecipitating IFNGR1 we found that IFNGR1 is polyubiquitinated through K48 linkage, which is consistent with proteasomal degradation. By labeling plasma membrane IFNGR1 using membrane impermeable biotin probe, we observed that the mature receptor is rapidly degraded, suggesting that ubiquitination and proteolysis is not the result of inefficient protein maturation but intrinsic to the signaling receptor. To determine which lysine residues were ubiquitinated, we performed site-directed mutagenesis and compared the stability of the wild-type and mutant IFNGR1. We found that mutation of three membrane proximal cytoplasmic lysine residues enhanced the half-life of the receptor in both epithelial and macrophage-like cells. To examine the role of ubiquitination in IFNGR1 signaling, we generated a stable IFNGR1 knockout cell line using the CRISPR-Cas9 system. Interestingly, although expression of the lysine mutant IFNGR1 resulted in increased IFNGR1 expression, we observed decreased phosphorylation of STAT1, and decreased interferon stimulated gene expression in response to IFN gamma.

Conclusion: Our experiments show that IFNGR1 is post transcriptionally destabilized by ubiquitination and proteasomal degradation. However, lysine ubiquitin acceptor sites in IFNGR1 were necessary for efficient IFN gamma STAT1 and gene induction, suggesting ubiquitin may play a role in receptor signaling. Further examination of the mechanism of ubiquitination and specific ubiquitin ligases that target IFNGR1 will provide new insight into IFN-γ signaling and may lead to novel therapeutic targets.
30-A Poster: Palmitate Rapidly Induces Mitochondrial Dysfunction in Primary Mouse Hepatocytes

Presenter: Canying Lu, Junior Faculty
Endocrinology and Metabolism

Research Interest: Bench

Mentors: Robert O'Doherty PhD

Funding Source: T32

Authors: Canying Lu MD, Amy Kakkanatt MD, Daniel Harmon PhD, Catherine Corey BS, Sruti Shiva PhD, Robert O’Doherty PhD

Introduction: Numerous studies have implicated saturated free fatty acids (FFAs) such as palmitate in the development of the metabolic abnormalities seen in obesity-associated hepatic steatosis. However, the underlying mechanisms of these are ill-defined. Mitochondria are crucial in hepatocyte metabolism as they are the primary site of fatty acid oxidation, and it has been proposed that their function is compromised in obesity. Herein, we hypothesize that an oversupply of adipose tissue-derived FFAs to the liver is a primary mechanism driving hepatic mitochondrial dysfunction.

Methods: Seahorse was used to measure oxygen consumption rate (OCR) in primary mouse hepatocytes treated with various FFA. Hepatocytes were isolated using a two-step collagenase perfusion technique from 10-12 week old healthy male C57Bl/6 mice. Hepatocytes were plated on collagen-coated Seahorse XF24 cell culture plates. After 1 hour recovery, hepatocytes were treated with vehicle or 0.05mM, 0.1mM, or 0.2mM FFA (palmitate, stearate, octanoate, oleate) for 16 hours at 37oC. Selected FFAs were chosen as the representative FFA of saturated/unsaturated and long/short chain FFA derived from lipolysis. Following incubation, a Seahorse MitoStress Test was performed and OCR was quantified following injection of the uncoupling agent FCCP.

Results: Hepatocytes treated with 0.2mM palmitate (16 carbon saturated fatty acid (C16:0)) demonstrated a 30.1% reduction in Maximal OCR compared to vehicle (0.714±0.416 vs 1.022±0.222, normalized to baseline and control, p<0.001). Hepatocytes treated with 0.2 mM palmitate also demonstrated a reduction in maximal OCR compared to 0.05mM and 0.1mM. Hepatocytes treated with 0.2mM stearate (18 carbon saturated fatty acid (C18:0)), octanoate (8 carbon saturated fatty acid (C8:0)) or oleate (18 carbon mono-unsaturated fatty acid (C18:1)) did not display any significant changes in maximal OCR.

Conclusion: Palmitate, a long chain saturated FFA (C16:0) and the major FFA derived from adipose tissue lipolysis, has a dose dependent negative effect on hepatocyte mitochondrial function in vitro (maximal ATP production potential). Furthermore, the inability of short chain saturated FFA octanoate and the long chain unsaturated FFA oleate indicate that the observed effect on mitochondrial maximal OCR are specific to palmitate. Indeed, the lack of an effect of another long chain FFA stearate (C18:0), which structurally differs from palmitate by only a single 2C addition to the carbon chain length, emphasizes this specificity. Results from our study indicate that palmitate has a unique ability to initiate hepatic mitochondrial dysfunction and suggests FFA derived from adipose tissue lipolysis may negatively affect liver function disproportionally.
**31-A Poster:** Th17 cells modulate the LN microenvironment through IL-17 dependent regulation of fibroblastic reticular cells

**Presenter:** Saikat Majumder, Post-Doctoral Fellow  
Rheumatology and Clinical Immunology  
**Research Interest:** Bench

**Mentors:** Mandy McGeachy PhD  
**Funding Source:** NIH RO1

**Authors:** Saikat Majumder PhD, Shankar Revu PhD, Fang Du PhD, Mandy McGeachy PhD

**Introduction:** Integrins play a critical role in the function and migration of Th17 cells in CNS, and blockade of inflammatory T cell migration is used therapeutically in multiple sclerosis. Our previously published data demonstrated a critical role for αvβ3 in driving encephalitogenic Th17 cell migration in experimental autoimmune encephalomyelitis (EAE), in an IL-23R-dependent manner.

**Methods:** Mouse inguinal lymph nodes were isolated from WT-EAE, IL17RA KO-EAE, IL-17A KO-EAE and IL23R KO-EAE mice and fibronectin levels were measured via q-PCR. We isolated and quantified the number of CD45-gp38+CD31-fibroblastic reticular cells (FRCs) from different groups of mice. We also analyzed FRCs marker by immunofluorescence in LNs.

**Results:** Herein, we show that fibronectin, a ligand for integrin αvβ3, is significantly upregulated in the dLNs of EAE mice. Strikingly, the expression of fibronectin in dLN was significantly reduced in IL23R-/- mice following immunization. Fibronectin expression increased in dLNs during the progression of EAE with similar kinetics but delayed peak compared to IL-17. Since IL23R regulates IL-17 production, we analyzed LN from IL-17-/- and IL17Ra-/- mice immunized for EAE, and observed a similar defect in fibronectin expression in the absence of IL-17 signaling. CD45-gp38+CD31-fibroblastic reticular cells (FRCs) in the T cell zone are the major producers of fibronectin in the dLNs, and these stromal cells expand during EAE. Although IL-17RA-/- LN appeared similarly enlarged following immunization, indicating an inflammatory response, the number of FRCs was decreased in immunized IL17Ra-/- LN, corresponding to decreased fibronectin.

**Conclusion:** Taken together, our data suggests that during priming of the immune response, and before migrating to their peripheral target tissue, Th17 cells modulate the local LN environment in which they are activated through production of IL-17 to promote FRCs expansion and induction of ECM. This could have long-term consequences in the host upon future infectious challenge, as well as influencing chronicity of Th17-mediated autoimmune disease.
32-A Poster: Universal Next-Generation Sequencing K65/M184 Drug Resistance Primers for Broad HIV Subtype Coverage

Presenter: Kevin McCormick, Post-Doctoral Fellow
Infectious Diseases

Research Interest: Bench

Mentors: Urvi Parikh PhD, John Mellors MD

Funding Source: USAID

Authors: Kevin McCormick PhD, Kerri Penrose MS, John Mellors MD, Urvi Parikh PhD

Introduction: Next-generation sequencing (NGS) has the potential to be adapted into a high-throughput, cost-efficient approach for sensitive HIV drug resistance surveillance during scale-up of antiretroviral therapy and rollout of pre-exposure prophylaxis. However, nucleotide mismatches in the primer binding sites between HIV subtypes compromise the efficient amplification of individual HIV genomes and limit the frequency of detecting minor drug resistance mutations. A novel approach is urgently needed to overcome the inefficient priming of unknown HIV subtypes for the development and implementation of a robust NGS assay that is cross-compatible with HIV Subtypes A, B, C and D.

Methods: We designed mixed-base NGS primers by building a consensus sequence using genomic data from clinical HIV subtype A, B, C and D isolates from the Los Alamos National Laboratory repository, and analyzing semi-conserved regions upstream and downstream from the target drug resistance sites, K65 and M184. Nucleotides that deviated between individual subtype sequences and this consensus by more than 5% were replaced with a mixed base (R [A & G], Y [T & C], or N [A, T, C, & G]) in our primer sets. The efficiency (cDNA yield) of our universal reverse primer was analyzed by extracting HIV RNA from cryopreserved HIV positive plasma from several subtypes and quantifying total cDNA copies (qPCR) after reverse transcription. The cDNA and semi-nested PCR forward primers were then used to prepare NGS libraries for determining the drug resistance detection limit using a previously characterized recombinant HIV subtype C drug resistant mixture panel.

Results: The cDNA yield from a recombinant subtype C virus template was equivalent using the mixed-based NGS primer or the subtype C-specific reverse primer. The mixed-base NGS primer successfully generated cDNA templates from HIV subtype A, B and D. Furthermore, both the mixed-base universal primer set and our previously characterized HIV subtype C primers accurately identified mutations present in the expected frequencies of our mixture panel.

Conclusion: Mixed-based primers efficiently amplified genomes from multiple HIV subtypes while maintaining the capacity to build NGS libraries in quantities sufficient for the identification of low frequency mutations. The use of mixed-base primers is a viable approach to overcome the obstacle of sequence diversity between HIV subtypes in NGS assays.
**33-A Poster:** Chronic stress is associated with altered urinary bladder neuronal distribution

**Presenter:** Bronagh McDonnell, Post-Doctoral Fellow  
Renal-Electrolyte  
**Research Interest:** Bench

**Mentors:** Lori Birder PhD  
**Funding Source:** RO1, R37

**Authors:** Bronagh McDonnell PhD, Aura Kullmann PhD, Larissa Rodriguez MD, Lori Birder PhD

**Introduction:** A hallmark of functional pain syndromes such as interstitial cystitis/bladder pain syndrome (IC/BPS) is pain in the absence of other demonstrable pathology. There is ample evidence that acute stress increases bladder pain and urgency in these individuals. Recent findings support increased bladder hyperalgesia and urinary frequency in rats exposed to chronic (10 day) water avoidance stress (WAS). In order to understand how changes in peripheral neural innervation may contribute to bladder hyperalgesia and pain in this model, we examined changes in sensory and autonomic innervation of the bladder.

**Methods:** Adult female Wistar-Kyoto rats (12 wks age, 200-250 gm) were placed on a pedestal in a water water-filled container. All procedures were conducted with approval of University of Pittsburgh Institutional Animal Care and Use Committee. Animals were exposed to WAS (or handled controls) one hr/day x10 days between hours 8 AM–12 PM to minimize circadian effects. To investigate the density and distribution of fibers in bladder we used immunocytochemistry to process bladder cross cryosections (20uM; postfixed following bladder removal from deeply anesthetized rats prior to sacrifice; n=3 rats), specifically against calcitonin gene related peptide (CGRP; sensory fibers) and tyrosine hydroxylase (TH; sympathetic fibers) and DAPI to label nuclei.

**Results:** Our findings reveal a significant increase (approx. 2-fold) in CGRP+ staining in WAS bladders (vs. control) with the greatest density within the bladder mucosa. We also find augmented TH+ staining (approx. 1.5-fold) staining in WAS bladders (vs. control), the latter surrounding the vasculature.

**Conclusion:** Alterations in both sensory and autonomic neural innervation in the bladder may represent an important mechanism that contributes to hypersensitivity/urgency in IC/BPS models of bladder pain.
34-A Poster: Urothelial barrier dysfunction sensitizes bladder afferents

Presenter: Nicolas Montalbetti, Junior Faculty
Renal-Electrolyte

Research Interest: Bench

Mentors: Marcelo Carattino PhD

Funding Source: None

Authors: Nicolas Montalbetti PhD, Anna Rued, Aura Kullmann PhD, Marcelo Carattino PhD

Introduction: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic voiding disorder that presents with pain in the urinary bladder and surrounding pelvic region. While the etiology of IC/BPS remains unknown, clinical evidence suggests that increased urothelial permeability to urine constituents contributes to the pathophysiology of this disease. In this regard, the message for claudin-2 (Cldn2), a tight-junction associated protein that forms paracellular pores, was found to be upregulated at least ninety fold in bladder biopsies of IC/BPS patients. We recently reported that the adenoviral-mediated overexpression of Cldn2 in the bladder urothelium increases the permeability to small charged solutes, triggers an inflammatory process in the bladder mucosa and lamina propria, and increases voiding frequency.

Methods: In the present study, we examined the consequence of increased urothelial permeability on bladder-derived pain and afferent excitability.

Results: Consistent with the presence of bladder-derived pain, rats overexpressing Cldn2 in the urothelium show hypersensitivity to von Frey filaments applied to the pelvic region, but not to the hind paw. Moreover, the overexpression of Cldn2 promotes the activation of the ERK pathway in spinal cord segments receiving bladder input, which we conceive is the result of noxious stimulation of afferent pathways. To determine whether the changes in bladder activity and pain observed in rats overexpressing Cldn2 result from altered afferent activity, we conducted patch-clamp studies with acutely isolated bladder sensory neurons. We found that ~30% of the bladder sensory neurons from rats overexpressing Cldn2, but not GFP, display spontaneous activity. In addition, the overexpression of Cldn2 in the urothelium increased the excitability of silent A-delta bladder afferent neurons. Because K+ channels are important determinants of neuronal excitability, we measured their mRNA levels in sensory neurons isolated from rats transduced with GFP or Cldn2. Single cell expression analysis showed upregulation of mRNA levels of Kv 2.2 and Kv 9.1, and downregulation of the alpha subunit of the large-conductance Ca2+-activated potassium (BK) channel in sensory neurons harvested from rats transduced with Cldn2.

Conclusion: In summary, our studies suggest that as a result of a leaky urothelium, the diffusion and accumulation of urinary solutes in the bladder interstitium sensitizes bladders afferents, promoting voiding at low filling volumes and pain.
**Introduction:** With No Lysine (WNK) kinases are serine/threonine (S/T) kinases with a uniquely positioned catalytic lysine required for chloride sensing. In metazoans, WNK1 is expressed ubiquitously and plays an important role in in cell chloride and volume regulation. However, WNK1 also regulates blood pressure and K+ homeostasis by controlling salt reabsorption in segments of the renal distal tubule, suggesting that it may have acquired new functions across evolution. The renin-angiotensin-aldosterone system (RAAS) targets WNK1 through specific sequences harbored in exons 11 and 12, two alternatively spliced cassette exons that are represented in kidney (Roy et al JCI 2015). Additionally, a kidney-specific, kinase-deficient isoform of WNK1 called KS-WNK1—defined by the presence of exon 4a—has been shown to regulate renal WNK pathway activity. We hypothesized that the unique kinase domain, alternative promoter usage, and splicing of WNK1 emerged at critical points in evolution to facilitate its role in cell volume control and renal electrolyte handling.

**Methods:** We employed phylogenetic reconstruction methods to analyze WNK1 gene evolution. We gathered nucleotide and protein sequences from the UCSC Genome Browser and NCBI databases. WNK1 protein sequences were then analyzed in SeaView to create multiple sequence alignments with Clustal Omega and phylogenetic trees with PhyML 3.0. The known structure of the WNK1 kinase domain (PDB ID 4Q2A) was used for homology modeling of ancestral WNK-like S/T kinase domain sequences in MODELLER.

**Results:** Exons 11 and 12 were only detected as far back as reptiles; The relatively recent appearance of these exons in evolution postdates the emergence of the RAAS, suggesting that aldosterone signaling may have applied a selective pressure that forced their incorporation into the WNK1 gene structure. The earliest we detect exon 4a is in coelacanth, a lobe-finned fish closely related to lungfish, the first vertebrate to crawl on land. Consistent with an ancient role of the kinase domain in cell-volume regulation, we detected sequences consistent with the WNK chloride-sensor in several protists. This preliminary finding challenges previous work suggesting that WNKs are solely present in multicellular organisms.

**Conclusion:** These observations suggest that WNK1 was first designed for cellular chloride and volume regulation in unicellular species, and was subsequently repurposed through alternative splicing and promoter usage for whole body salt and volume homeostasis during kidney development in metazoans. Critical elements of the WNK1 gene emerged during a key point in kidney evolution; namely, during the transition from water to land for temporary and permanent inhabitance.
Introduction: Pulmonary hypertension (PH) is a neglected, life-threatening vascular disease with mysterious molecular origins. It results in elevated blood pressure in pulmonary arteries, leading to right heart failure, multi-organ dysfunction, and often death. Approved medications for PH act through vasodilation primarily, but they neither prevent nor reverse the disease. Thus there is an imperative need for developing new drugs for PH. Evidence suggests parallels in the pathogenesis of cancer and PH and repurposing of chemotherapeutics for PH has been suggested. However, manual drug screening is slow and labor-intensive. Given the existing large scale -omics data sets available for cancer, it may be possible to apply big data analysis in cancer to PH, thus making a computational repurposing of chemotherapeutics feasible for PH.

Methods: RNA sequencing data from >800 cancer cell lines exposed to 368 chemotherapies [via CTRP (Cancer Therapeutics Response Portal) and CCLE (Cancer Cell Line Encyclopedia) databases] were combined with a compilation of gene clusters important in PH using a novel computational algorithm, EDDY (Evaluating Differential DependencY), to define the re-wiring of gene dependency networks of these PH gene clusters in response to specific chemotherapies.

Results: We found six drugs that were already in clinical trials and ranked particularly highly in terms of most substantial re-wiring across PH clusters in general, with specific overlap with activity in two particular “hot-spot” gene clusters (cluster 15 and 16) that have never been linked to PH experimentally. These drugs were I-BET151/I-BET762, MK-1775, NVP-231 momelotinib, and crizotinib. The effects of the top ranked drugs, the BET inhibitors I-BET151/762 were further interrogated in vitro in conditions known to be triggers of PH, such as exposure to hypoxia and the inflammatory cytokine IL-1ß in cultured human pulmonary endothelial and smooth muscle cells. Both hypoxia and IL-1ß exposure-induced changes in cluster 15 gene expression and downstream inflammation were found to be reversed by I-BET151/762.

Conclusion: We identified specific chemotherapies that modulate PH gene clusters and relevant vascular pathophenotypes. We further plan to define the therapeutic actions of these drugs, starting with I-BET151/762, in PH and delineate the molecular actions of these hot-spot gene clusters. If successful, this work would establish the validity of a computational pipeline designed to repurpose drugs for a broad range of diseases not possible to date.
37-A Poster: Does the E138A mutation in ASPIRE seroconverters affect susceptibility to Dapivirine?

Presenter: Kerri Penrose, Junior Faculty
Infectious Diseases

Research Interest: Bench

Mentors: John Mellors MD

Funding Source: None

Authors: Kerri Penrose MSc, Breanna Goetz BS, Kelley Gordon BS, Daniel Szydlo MSc, Marla Husnik MSc, Thesla Palanee-Phillips PhD, Jared Baeten MD, John Mellors MD, Urvi Parikh PhD

Introduction: The reverse transcriptase (RT) polymorphism E138A occurs naturally in 5% of treatment-naïve HIV-1-subtype C-infected individuals, but is also selected by the diarylpyrimidine (DAPY) class of NNRTIs causing 3-fold resistance to etravirine and rilpivirine. E138A could reduce the protective efficacy of the vaginal ring candidate dapivirine (DPV) in preventing HIV-1 infection. DPV resistance was investigated among recombinant subtype C viruses with E138A derived from seroconverters in ASPIRE.

Methods: ASPIRE was a safety and effectiveness study of a DPV vaginal ring for HIV-1 prevention conducted at 15 sites in South Africa, Zimbabwe, Malawi and Uganda. Population sequencing of protease and RT (amino acids 1-560) was performed on plasma samples from 164 seroconverters with HIV-1 RNA levels =200 copies/ml using an in-house assay. Drug resistance mutations (DRM) were identified using the Stanford HIVdb program v7.0. DPV susceptibility of plasma-derived recombinant HIV-1 containing bulk-cloned full-length RT sequences from ASPIRE seroconverters with E138A was determined in TZM-bl cells. Fold-change (FC) values were calculated using a mean IC50 from a matched number of seroconverters without E138A from each arm. Statistical significance was calculated using Fisher's Exact and Likelihood Ratio tests.

Results: The frequency of E138A was not significantly different (p=1.0) between seroconverters in the DPV arm (3 of 68; 4.4%) vs. placebo arm (5 of 96; 5.2%) of ASPIRE. Of participants with E138A, 2 of 3 from the DPV arm (2.1-FC and 6-FC) and 2 of 5 from the placebo arm (3.3-FC and 3.6-FC) had significantly (p<0.05) higher IC50 compared to participants with wild type virus. Mean IC50 values for E138A-containing HIV-1 from the DPV arm (3 nM) was not significantly different from the placebo arm (2.2 nM).

Conclusion: E138A is a naturally occurring polymorphism in HIV subtype C that is associated with modest reductions in DPV susceptibility in some RT backgrounds but not others. The frequency and extent of reduced susceptibility associated with E138A as the major variant was independent of the ASPIRE study arm. Although the low frequency of 138A limited the sample size, these phenotypic data provide reassurance that the E138A mutation was not selected by the DPV vaginal ring and is unlikely to reduce efficacy of the DPV vaginal ring for HIV-1 prevention.
**38-A Poster:** Rosuvastatin reduces systemic inflammation in HIV-associated chronic obstructive pulmonary disease

**Presenter:** Shulin Qin, Junior Faculty  
**Research Interest:** Bench Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD, MS  
**Funding Source:** R34HL117344, R01HL090339, R01HL083461 (AM)

**Authors:** Shulin Qin PhD, Meghan Fitzpatrick MD, Marnie Bertolet PhD, Lawrence Kingsley PhD, Nicolas Leo BS, Cathy Kessinger RN, Heather Michael BS, Deborah McMahon MD, Renee Weinman BS, Stephen Stone BA, J. Kenneth Leader PhD, Eric Kleerup MD, Laurence Huang MD, Stephen Wisniewski, PhD

**Introduction:** Chronic obstructive pulmonary disease (COPD) is more prevalent in HIV-infected individuals and is associated with persistent inflammation. Therapies unique to HIV-associated COPD are lacking. Rosuvastatin, a HMG Co-A reductase inhibitor, exerts anti-inflammatory effects. As part of a pilot study of the effect of rosuvastatin on lung function, we also analyzed its impact on systemic inflammation and markers of vascular dysfunction as well as relationship of inflammatory mediators to change in lung function.

**Methods:** HIV-infected individuals with abnormal lung function were recruited for a triple blinded, randomized, placebo-controlled clinical study. Participants were randomized to 24 weeks of placebo (n=11) or rosuvastatin (n=11) using an adaptive randomization based on change in peripheral C-reactive protein levels at 30 days of treatment. Expression levels of inflammatory biomarkers and the vascular dysfunction marker endothelin-1 (ET1) in sera and PBMCs were measured by ELISA and real-time RT-PCR at baseline and 24 weeks, respectively. Changes in these inflammatory biomarkers between baseline and 24 weeks were analyzed separately in the two groups using Wilcoxon signed-rank test and relationships between biomarkers and lung function were analyzed using Spearman rank correlation.

**Results:** Inflammatory mediators CCL8, IL-6, and vascular dysfunction marker ET1 expression levels decreased over 24 weeks in the rosuvastatin group, but they did not change significantly in the placebo group. The immune cell activation markers sCD14 and sCD163 expression levels significantly increased over 24 weeks in the placebo group, but both levels remained similar in the rosuvastatin group. Correlation analysis results have shown that plasma IL-6 or sCD163 levels were negatively correlated with FEV1 %-predicted, respectively (rho=-0.594, p=0.015 and rho=-0.535, p=0.033), and also plasma sCD163 levels were negatively associated with DLco %-predicted (rho=-0.577, p=0.019) in the rosuvastatin group.

**Conclusion:** In this study, use of rosuvastatin for 24 weeks appeared to reduce systemic inflammation and improve vascular function in HIV-infected individuals with abnormal lung function. Systemic inflammation could play an important role in the pathogenesis and progression of HIV-associated COPD. As rosuvastatin was associated with improvements in lung function in the parent trial, the results suggest potential mechanisms of benefit.
**39-A Poster:** IL-17 receptor signaling in kidney epithelial cells is important in protection against disseminated candidiasis

**Presenter:** Kritika Ramani, Post-Doctoral Fellow  
Rheumatology and Clinical Immunology

**Research Interest:** Bench

**Mentors:** Partha Biswas PhD

**Funding Source:** None

**Authors:** Kritika Ramani PhD, Partha Biswas PhD

**Introduction:** Disseminated candidiasis is a nosocomial infection with up to 40% mortality rates. Fungal invasion in the kidney is a known cause of renal failure in a significant number of patients. We have previously shown that interleukin-17 (IL-17), a recently identified inflammatory cytokine has a tissue protective role via the up-regulation of the kallikrein-kinin system in disseminated candidiasis. Although IL-17 producing cells were detected in the infected kidneys, the identity of IL-17 responsive cell types in protection against fungal invasion in the kidney unknown.

**Methods:** Using bone marrow chimeras, we interrogated the requirement for IL-17RA in the hematopoietic versus non-hematopoietic compartments. To determine the specific role of IL-17RA in kidney resident cells, we generated mice with conditional deletion of IL-17RA in the proximal and distal tubular kidney epithelial cells (Cdh16Cre IL17RAflx). Renal immune responses against fungal infection were measured by flow cytometry and gene expression.

**Results:** From our bone marrow chimera experiments, we found that signaling through IL-17RA in the non-hematopoietic compartment was crucial in the protection against disseminated candidiasis. We also demonstrated that abrogation of IL-17 receptor signaling in Cdh16Cre IL17RAflx mice led to decreased survival following infection with C. albicans. At early time points (day 5) Cdh16Cre IL17RAflx mice had increased fungal burden. The fungal clearance data was corroborated by diminished antimicrobial peptide and chemokine gene expression in the Cdh16Cre IL17RAflx mice, however the inflammatory cell influx was unchanged. At a later time point (day 7) we observed a significant increase in damage-associated markers such as NGAL in the kidneys of Cdh16Cre IL17RAflx mice, correlating with increased susceptibility to infection. We also show that IL-17R signaling in renal epithelial cells up regulated multiple genes of kallikrien-kinin system, known to play a critical role in renal protection against disseminated candidiasis.

**Conclusion:** Our data indicate a kidney specific role of IL-17 signaling in renal protection against disseminated candidiasis. In the long run, these results may inspire the development of worthwhile therapeutic approaches in the treatment of this fatal nosocomial disease.
Introduction: The JAK/STAT signaling pathway plays a critical role in early stages of T helper (Th) cell subset differentiation. Th17 cells are a major subset of Th cells which have been linked to the emergence of many autoimmune and inflammatory conditions. Conceivably, early differentiation and expansion of these cells rely on key cytokine-receptors which signal through STAT3, including IL-6R and IL-23R. Thus, development of drugs that target STAT3 or its upstream receptors are a major research focus to alleviate disease. However, the role of STAT3 signaling in effector/memory Th17 cells remain elusive.

Methods: Here, we developed a model to study the role of STAT3 in effector/memory Th17 cells in EAE, an animal model of multiple sclerosis.

Results: Our data show that mice lacking STAT3 in effector Th17 cells are resistant to EAE development. Strikingly, we demonstrate that in Th17 cells, STAT3 is not required for Th17 lineage-commitment or its cytokine expression in-vivo, but rather is pivotal for cell survival. Bioinformatics analysis of effector Th17 cell transcriptome from draining lymph nodes at day 10 (onset) of EAE revealed that STAT3 deficient Th17 cells had increased expression of genes associated with specific cell-death pathways, and decreased expression of gene involved in cell proliferation and T cell-mediated tissue damage.

Conclusion: Our data reveal a hitherto unappreciated mechanism for STAT3 in effector Th17 cells which have major implications for disease therapies and should be explored in future studies.
**41-A Poster:** CD28 co-stimulation negatively regulates differentiation of human but not mouse Th17 cells

**Presenter:** Shankar Revu, Post-Doctoral Fellow  
Research Interest: Bench Rheumatology and Clinical Immunology

**Mentors:** Mandy McGeachy PhD  
Funding Source: Rheumatology Research Foundation

**Authors:** Shankar Revu PhD, Jing Wu MD PhD, Matthew Henkel MSc, Gerard Hernandez MSc, Mandy McGeachy PhD

**Introduction:** Th17 cells are important for protection from extracellular bacterial and fungal pathogens as well as homeostasis of commensal microbes. However, Th17 cells are perhaps best known for their roles in driving autoimmune inflammatory diseases, and blockade of IL-17 is now approved for therapy of psoriasis and ankylosing spondylitis and is being tested in other diseases. Differentiation of Th17 cells is not straightforward, and requires multiple inducing cytokines. Furthermore, study of Th17 cells in humans has been complicated by the difficulty of obtaining high frequencies of IL-17 producing cells in vitro, and the optimal conditions for differentiating human Th17 cells remain controversial. CD28 is considered a critical costimulatory molecule for T-cell activation and is routinely added to T cell activation cultures along with anti-CD3. In this study we investigated on how CD28 co-stimulation regulates differentiation of human Th17 cells.

**Methods:** Human CD4 naive T cells were isolated from healthy donor peripheral blood mononuclear cells (PBMCs). Cells were cultured on plate bound anti-CD3 coated 96 well plate in the presence of recombinant IL23+IL1b to induce Th17 cells, and with or without anti-CD28. Cells were cultured for 7 days and treated with PMA+Ionomycin+Golgi for 4 hours prior to cell surface and cytokine staining. Flow cytometry and qRT-PCR analysis was performed to determine Th17 phenotype as detected by IL17 and ROR?t expression.

**Results:** We report here the surprising finding that CD28 co-stimulation suppressed differentiation of Th17 cells in a dose dependent manner, as detected by IL-17 and ROR?t. Although activation of T cells with anti-CD3 alone resulted few proliferating CD45RO+ activated T cells, as expected, this was not the case when Th17-inducing cytokines were added. Hence, it appears that cytokines can compensate for absence of CD28 costimulation in generating Th17 cells. We are currently testing response of Th17 cells generated without CD28 to secondary restimulation to confirm preliminary results that these cells are not anergic and maintain Th17 phenotype. We are also investigating mechanisms by which CD28 suppressed Th17 differentiation in human T cells. In contrast to these data, in mouse Th17 cultures the addition of CD28 costimulation resulted in enhanced responses, as previously reported.

**Conclusion:** In contrast to human, addition of anti-CD28 to mouse Th17 cultures resulted in enhanced responses, fitting with known differences in CD28 costimulation effects between mouse and human. Together, these data provide new insight into mechanisms that regulate the generation of human Th17 cells, and have implications for approaches to target Th17 cells in autoimmune disease.
**Introduction:** Influenza is a common respiratory virus that results in up to 500,000 deaths worldwide each year. Influenza is often complicated by secondary bacterial infections of the lung, such as Staphylococcus aureus (SA). Secondary bacterial pneumonia is responsible for the severe morbidity and mortality observed during influenza infection. S. aureus bacterial super-infection of the lung is increasing in prevalence and can be difficult to treat. IL-33 is a cytokine in the IL-1 family that stimulates the development of Type 2 immune cells. We examined the role of IL-33 during influenza A and S. aureus co-infection.

**Methods:** Wild-type mice were challenged with influenza A H1N1 (PR/8/34) followed by challenge with MRSA at 6 days post-influenza. Bacterial burden, gene expression and cytokine production of IL-33 were determined. Wild-type and Rag2/Il2rg/-/- mice were challenged with Influenza A H1N1 (PR/8/34) followed by challenge with MRSA at 6 days post-influenza. Mice received recombinant IL-33 prior to MRSA challenge. Lung inflammation, bacterial burden, gene expression, and cytokine production were determined. In addition, wild-type mice received an anti-neutrophil antibody (Ly6G) and lung inflammation, bacterial burden, gene expression, and cytokine production were assessed.

**Results:** First, we found that bacterial burden was increased and IL-33 was decreased in mice super-infected with Influenza A and MRSA compared to mice singularly infected with MRSA. Next, studies demonstrated that both wild-type and Rag2/Il2rg/-/- mice that received IL-33 prior to MRSA challenge during influenza had significantly decreased bacterial burden and lung inflammation compared to controls. Finally, we found that IL-33 treatment results in neutrophil recruitment to the lung associated with improved bacterial clearance and blocking neutrophils reverses this enhanced clearance of bacteria.

**Conclusion:** These data indicate that IL-33 is critical to clearance of MRSA during influenza/MRSA co-infection and helps protect against bacterial super-infection. A potential mechanism by which IL-33 is advantageous to bacterial host defense is through neutrophil recruitment to the lung. Identification of new pathways in the pathogenesis of bacterial pneumonia could potentially lead to novel therapeutic targets with the goal of improving respiratory health.
Introduction: Acid-sensing ion channels (ASICs) are trimeric proton-gated cation permeable ion channels expressed in neurons that contribute to diverse physiological processes including nociception, mechanosensation, synaptic plasticity, memory, and learning.

Methods: Here we employed site-directed mutagenesis and electrophysiology to investigate the mechanism of inhibition of ASICs by diminazene. This compound inhibits mouse ASIC1a and ASIC3 with a half-maximal inhibitory concentration (IC50) of 2.4 µM and 1.5 µM, respectively. At first, we investigated whether diminazene binds to a hexagonal array of acidic residues formed by Glu79 and Glu416 in the lower palm domain, which previously was shown to facilitate pore opening in response to extracellular acidification.

Results: Diminazene inhibited ASIC1a E79Q and E416Q mutants with an IC50 of 18 µM and 14 µM, respectively. Likewise, the neutralization of Glu79 (E79Q) on ASIC3 shifted diminazene IC50 from 1.5 µM to 5.6 µM. On the contrary, the neutralization of residues in the acidic pocket of ASIC1a, a cluster of negatively charged residues in the extracellular region that serves as binding site for psalmotoxin, did not change diminazene IC50. Although mutations at positions 79 and 416 weaken diminazene block, the relatively small changes observed suggests that these residues do not encompass the primary diminazene binding site. Because of its high polarity, we assessed whether diminazene inhibits ASICs by blocking the ion permeation pathway. A hallmark of pore blockers is that their affinity varies with membrane voltage. Consistent with the notion that diminazene binds to a site within the membrane electric field, diminazene IC50 showed a strong dependence with the membrane potential. Moreover, a Gly to Ala mutation at position 438 in the pore of ASIC1a increased diminazene IC50 by two orders of magnitude. This result suggests that Gly438 is part of the diminazene binding site.

Conclusion: Taken together, our results indicate that diminazene inhibits ASICs by blocking the flow of ions through the pore of the channel. This finding provides a foundation for the development of more selective and potent ASIC pore blockers.
**Poster Abstracts**

**44-A Poster:** The aldosterone-repressible protein DCNL4 promotes WNK kinase degradation via the KLHL3/CUL3 complex

**Presenter:** Ankita Roy, Junior Faculty  
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** Arohan Subramanya MD  
Funding Source: R01

**Authors:** Ankita Roy PhD, Lubika Nkashama BS, Michael Butterworth PhD, Thomas Kleyman MD, Arohan Subramanya MD

**Introduction:** WNK kinases coordinate NaCl and K+ transport in the aldosterone-sensitive distal nephron (ASDN). In intercalated cells of the ASDN, WNK1 expression is increased to augment luminal K+ secretion via flow-activated BK channels. WNK abundance is primarily controlled by the KLHL3/CUL3 complex, a cullin-RING E3 ligase (CRL) that ubiquitylates the WNKs, marking them for degradation. Little is known about the mechanisms that physiologically regulate KLHL3/CUL3 complex activity. Mammalian DCN-like (DCNL) proteins are a family of five evolutionarily conserved CRL co-activators that promote cullin activity through neddylation. Of these proteins, DCNL4 was identified as a candidate stimulator of KLHL3/CUL3 complex activity and WNK substrate turnover, as kidney RNAseq databases noted DCNL4 expression in the distal tubule, and microRNA prediction algorithms identified DCNL4 as a target of miR-27, an aldosterone-induced microRNA whose activity is linked to cardiovascular disease. Thus, we hypothesized that aldosterone-mediated repression of DCNL4 should downregulate KLHL3/CUL3 activity, increasing WNK1 expression and activity in the distal nephron.

**Methods:** We evaluated DCNL4 expression in the mouse kidney by RT-PCR, immunostaining, and immunoblot in mice treated with high and low K+ diets. DCNL4 was transiently coexpressed with KLHL3/CUL3 and WNKs in 293 cells to assess CUL3 neddylation status and WNK turnover by CHX chase. Mouse cortical collecting duct cells were treated with aldo (50nM) or a miR27 mimic and DCNL4 mRNA was quantified by qRT-PCR.

**Results:** Renal DCNL4 was detectable by RT-PCR & immunoblot. Under standard dietary conditions, DCNL4 antibodies recognized a modest signal in pendrin-positive intercalated cells. This signal was strongly upregulated with dietary K+ restriction, while WNK kinase expression was downregulated in ICs under the same conditions, suggesting reciprocal regulation. In cell culture models, DCNL4 enhanced CUL3 neddylation. When coexpressed with KLHL3/CUL3, DCNL4 strongly downregulated WNK abundance via enhanced proteasomal degradation. Consistent with KLHL3/CUL3 dependency, DCNL4 did not reduce WNK1 abundance when it was coexpressed with hypertension-associated KLHL3 mutants that disconnect WNK kinases from CUL3. In mCCD cells, DCNL4 mRNA was strongly reduced by aldo and miR27 mimics.

**Conclusion:** These data support a model in which DCN-like proteins trigger the degradation of WNK kinases by potentiating KLHL3/CUL3 complex activity through neddylation, an effect that is enhanced by hypokalemia. MicroRNA-mediated downregulation of KLHL3/CUL3/DCNL4 complexes might represent a novel mechanism by which aldosterone can specifically augment WNK signaling in intercalated cells of the distal nephron. Our findings indicate that DCNL4 orchestrates a WNK-dependent K+ secretory response in intercalated cells of the ASDN.
**45-A Poster:** The Role of Pore-lining Residues of MEC-4 and MEC-10 in the Channel’s Response to Shear Stress

**Presenter:** Shujie Shi, Junior Faculty  
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** None

**Funding Source:** K01, K37, P30

**Authors:** Shujie Shi PhD, Thomas Kleyman MD

**Introduction:** In the nematode Caenorhabditis elegans, gentle body touch is sensed via a multi-protein mechanotransduction apparatus expressed in the worm’s touch receptor neurons. At the core of this mechanotransduction apparatus is a mechanosensitive ion channel formed by two homologous protein, MEC-4 and MEC-10. Like other members of the epithelial Na+ channel (ENaC)/degenerin family, the channel’s pore is primarily lined by the second transmembrane helixes (TM2) of MEC-4 and MEC-10. Strikingly, there are nine and four touch-insensitive mutations within the MEC-4 TM2 and MEC-10 TM2, respectively, highlighting the importance of the pore-lining residues in transmitting gating signals.

**Methods:** To explore the role of the pore-lining residues of MEC-4 and MEC-10 in the channel’s regulation by mechanical forces, we introduced point mutations at the specific sites within the MEC-4 TM2 or MEC-10 TM2 and examined its response to LSS in Xenopus oocytes.

**Results:** When expressed in Xenopus oocytes, the MEC-4/MEC-10 channel is activated by flow-mediated laminar shear stress (LSS), and both MEC-4 and MEC-10 are required for a robust LSS response. We observed that the LSS response was largely diminished by touch-insensitive mec-10 alleles that introduce charged residues into the channel’s pore. Both the magnitude and kinetics of channel action by LSS were altered when mutations were introduced at specific sites within MEC-4 TM2. In addition, we found that channels with high intrinsic Po (MEC-4 A713D, or MEC-4 A713C modified with MTSES) showed reduced response to LSS.

**Conclusion:** Together, our results support an essential role of the pore-forming regions of MEC-4 and MEC-10 in channel gating in response to mechanical stimuli.
**46-A Poster:** TBK1/IKKe Signaling Is a Novel Therapeutic Target In Multiple Myeloma-Induced Bone Disease

**Presenter:** Quanhong Sun, Junior Faculty
Hematology/Oncology

**Mentors:** Deborah Galson PhD

**Authors:** Quanhong Sun PhD, Peng Zhang PhD, Deidra Balchak BS, Juraj Adamik PhD, Valentina Marchica PhD, Nicola Giuliani PhD, Rebecca Silbermann MD, G. David Roodman PhD, Deborah Galson PhD

**Research Interest:** Bench

**Funding Source:** NIH

**Introduction:** Multiple myeloma (MM) is the most frequent cancer to involve the skeleton and remains incurable for most patients, thus novel therapies are needed. MM bone disease is characterized by osteolytic lesions that contribute significantly to patient morbidity and mortality. We showed that TBK1 signaling is a novel pathway that increases osteoclast (OCL) formation in Paget's disease, an inflammatory bone disease. Therefore, we hypothesized that TBK1 plays a similar role in MM induction of OCL.

**Methods:** We employed qPCR, western blotting, transfection, transduction, immunofluorescence, XTT and shRNA knockdown to examine this hypothesis.

**Results:** We found that MM conditioned media (MM-CM) dose-dependently increased bone marrow monocyte (BMM) expression of activated TBK1 protein and enhanced RANKL-driven OCL formation. TBK1 knockdown by shRNA transduction into BMM significantly attenuated the ability of MM-CM to increase OCL differentiation without altering OCL differentiation in control media. However, the TBK1/IKKe inhibitors BX795 and Amllexanox (Amlx) blocked normal and MM-enhanced OCL formation. Importantly, TBK1 mRNA expression in CD138+ plasma cells (PC) isolated from MM or PC leukemia patients is significantly higher as compared to PC from Monoclonal Gammopathy of Undetermined Significance (MGUS) patients. Therefore, we tested whether targeting the TBK1/IKKe signaling pathways would also affect MM cells. We found that BX795 and Amlx strongly decreased the viability of several MM cell lines and primary MM cells via induction of apoptosis. Amlx is less potent than BX795, but a more specific nontoxic inhibitor. Therefore, only Amlx was used in the following studies. Amlx treatment of MM cell lines also induced a G1/S blockade, increased translation of the dominant-negative C/EBP-?-LIP isoform and increased autophagy (detected by increased LC3II). The positive-acting C/EBP-?-LAP isoform was previously shown to be a critical transcription factor for MM viability. C/EBP-?-LIP might also be responsible for the increased autophagy. Importantly, Amlx also enhanced the effectiveness of the proteasome inhibitor bortezomib and the immunomodulatory drugs (IMiDs), Lenalidomide and Pomalidomide, to kill MM cells in culture. Amlx did not affect the viability of primary BMM, bone marrow stromal cells (BMSC), or splenocytes. Further, Amlx blocked primary BMSC expression of IL-6 and RANKL, thereby decreasing BMSC support of MM survival and OCL differentiation. Amlx pretreatment of BMSC and MC4 cells also decreased VCAM1 expression and reduced MM cell adhesion, another mechanism for reduced MM support.

**Conclusion:** These data suggest that targeting TBK1/IKKe signaling may decrease MM bone disease by slowing MM growth, directly and indirectly, and preventing MM-induced osteolysis.
47-A Poster: Rapamycin Inhibits Calcification: Role of TNAP and Autophagy

Presenter: Swastika Sur, Post-Doctoral Fellow
Cardiology

Research Interest: Bench

Mentors: Cynthia St Hilaire PhD

Funding Source: NIH K22HL117917

Authors: Swastika Sur PhD, Evelyn Garchar MS, Luis Hortells PhD, Cynthia St Hilaire PhD

Introduction: Vascular calcification is an actively regulated biological process, and is associated with increased cardiovascular risk. Arterial Calcification due to Deficiency of CD73 (ACDC) is an autosomal recessive disease that is caused by mutations in the NT5E gene, which encodes for the enzyme CD73. ACDC affects the arteries of the lower limbs, causing medial-layer calcification. CD73 converts extracellular AMP to adenosine. Previously, we showed that loss of CD73 activity leads to compensatory increase in tissue-nonspecific alkaline phosphatase (TNAP) activity, which induces ectopic calcification. In vitro and in vivo disease modeling identified that mTOR inhibitor rapamycin significantly reduced TNAP expression and calcification. The mechanism by which rapamycin inhibits both TNAP expression and calcification remains unknown. Hypothesis: We hypothesize that in the absence of CD73 activity, activation of the mTOR pathway induces transcription factors (TFs) to upregulate TNAP gene expression, which leads to calcification that can be inhibited by rapamycin induced autophagy.

Methods: Transfac database was used to screen the TNAP promoter to identify TFs that may upregulate its expression. Control and ACDC fibroblasts, and CASMCs will be cultured under osteogenic condition and the temporal expression of TFs having sites on the TNAP promoter will be quantified. TNAP promoter reporter construct and chromatin immunoprecipitation will be used to confirm TF binding to the TNAP promoter. Effect of rapamycin on TNAP gene expression, activity, and calcification will be quantified. To determine if the anti-calcific effect of rapamycin is due to induction of autophagy, we will use pharmacological and biochemical inducers and inhibitors of autophagy in our in vitro calcification assay. Further, we are generating mice to study the role of mTORC1 in medial layer calcification.

Results: ACDC, but not control, fibroblasts display increased TNAP expression and activity. TNAP promoter screening identified several TF binding sites and RT-qPCR suggests that KLF9 and XBP1 are temporally regulated in a manner which could suggest a role in TNAP gene expression. Rapamycin inhibited osteogenic media induced TNAP activity and calcification in ACDCs and CASMCs, as did specific induction of autophagy using a Beclin-1 derived peptide.

Conclusion: These results show that osteogenic media upregulates KLF9 and XBP1, which may increase TNAP expression in ACDC and CASMCs. Rapamycin decreases TNAP expression and inhibits calcification. Under osteogenic stimulation, rapamycin and activation of autophagy inhibit calcification in these cells, suggesting that the anti-calcific effects of rapamycin could be due to induction of autophagy.
**Poster Abstracts**

**48-A Poster:** Suppression of Nrf2 Activity May Lead to AKI-to-CKD Progression

**Presenter:** Roderick Tan, Junior Faculty
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** None

**Funding Source:** AHA Fellow-to-Faculty Award

**Authors:** Brittney Rush BS, Sarah Small, Roderick Tan MD PhD

**Introduction:** Acute kidney injury (AKI) remains a significant problem worldwide. While some patients recover after AKI, others progress to or are predisposed to chronic kidney disease (CKD) and dialysis dependence. Greater understanding of the molecular mechanisms influencing these disparate outcomes would have significant therapeutic implications. The Keap1/Nrf2 pathway regulates over 200 cytoprotective genes and is highly expressed in normal kidney tubular epithelium. Keap1 is an inhibitor of Nrf2 and directs Nrf2 for ubiquitination and proteasomal degradation. During oxidative stress injuries such as AKI, Keap1 releases Nrf2, which translocates to the nucleus to upregulate target genes. Previous studies have shown that Nrf2 is critical for renal protection from AKI due to ischemia-reperfusion and that pharmacologic Nrf2 enhancement reduces AKI severity. These investigations also found that Nrf2 activity is enhanced after AKI, perhaps as an attempt to protect from further injury and restore normal function. Our own research has shown that genetic enhancement of Nrf2 signaling (using a Keap1 hypomorphic mouse) did not affect acute tubular injury after a severe ischemic period, but enhanced recovery and ameliorated AKI-to-CKD progression. In contrast to previous studies, our injury model led to decreased, not enhanced, Nrf2 activity, which was partially improved in Keap1 hypomorph mice. We hypothesized that severe AKI leads to this decreased Nrf2 activity, and that maintenance of Nrf2 activity is a key mechanism explaining whether AKI progresses to CKD.

**Methods:** We subjected wild type C57Bl/6 mice to mild, moderate and severe ischemia/reperfusion injury and examined serum creatinine and renal histology at various timepoints ranging from the acute to chronic phases of injury. Nrf2 signals were determined by quantitative real-time PCR (qRT-PCR) for specific Nrf2 target genes, including NQO1, GSTM1, and GSTP1. Targets were also validated with western blots.

**Results:** Mild AKI was associated with transient elevations in serum creatinine and minimal histologic injury. Severe injuries were characterized by creatinine elevations that continued to worsen over time as well as the development of fibrosis. Mild injuries were associated with an enhancement of Nrf2-associated target gene transcription when assessed by qRT-PCR, while severe injuries were associated with a suppression of Nrf2 activity.

**Conclusion:** Our data shows that there is a threshold effect at which the severity of AKI leads to the development of progressive CKD. One underlying mechanism for this may be the loss of protective Nrf2 signals during severe injury. Enhancement of Nrf2 activity prior to and after injury may prevent AKI-to-CKD progression.
**49-A Poster:** Gcn5l1 promotes enhanced cardiac fatty acid oxidation through acetylation of mitochondrial proteins

**Presenter:** Dharendra Thapa, Post-Doctoral Fellow Cardiology

**Research Interest:** Bench Cardiology

**Mentors:** Iain Scott PhD

**Funding Source:** K22

**Authors:** Dharendra Thapa PhD, Manling Zhang MD, Danielle Guimarães PhD, Michael Stoner BS, Robert O’Doherty PhD, Sruti Shiva PhD, Iain Scott PhD

**Introduction:** Mitochondrial dysfunction and impaired energy production have been implicated in obesity and diabetes. Lysine acetylation is a reversible post-translational modification, and is particularly important in the regulation of mitochondrial metabolic enzymes. Acetylation uses acetyl-CoA derived from fuel substrate metabolism as a co-factor, which links nutritional inputs to metabolic activity. We hypothesize that Gcn5l1 is required for the acetylation of mitochondrial fatty acid oxidation (FAO) proteins during high fat diet feeding. Further, we postulate the acetylation of FAO proteins regulates mitochondrial bioenergetics during diet induced obesity.

**Methods:** To identify the role of Gcn5l1 in cardiac mitochondrial protein acetylation, immunoprecipitation with acetylated lysine antibodies was performed to assess the acetylation status of FAO proteins. Western blots and qPCR were performed to quantitate protein and mRNA expression levels. Further, mitochondrial bioenergetics assessments were conducted to examine the role of Gcn5l1 in mitochondrial function.

**Results:** We found that there was a significant increase in cardiac mitochondrial protein acetylation in mice fed with a long-term high fat diet, and that this change correlated with an increase in the abundance of the mitochondrial acetyltransferase-related protein Gcn5l1. Further, we show that the acetylation status of two mitochondrial fatty acid oxidation enzymes was significantly upregulated in high fat diet mice, and that this was linked to an increase in their enzymatic activity. Finally, we demonstrate that the acetylation of mitochondrial fatty acid oxidation proteins is decreased following Gcn5l1 knockdown, and that reduced acetylation leads to diminished fatty acid oxidation in cultured H9C2 cells.

**Conclusion:** Based on our findings, we conclude that lysine acetylation promotes fatty acid oxidation in the heart, and that this modification is regulated in part by the activity of Gcn5l1. Examination of potential interacting partners of Gcn5l1 in diabetic hearts will further validate the critical role of this protein in mitochondrial protein acetylation and bioenergetics.
**50-A Poster:** Age-related changes in lysosomal function

**Presenter:** Steven Truschel, Junior Faculty
**Research Interest:** Bench Renal-Electrolyte

**Mentors:** None
**Funding Source:** R01

**Authors:** Steven Truschel PhD, Gerard Apodaca PhD, Lori Birder PhD

**Introduction:** Age-related changes in cellular function can lead to various human pathologies including cancer, diabetes, and neurodegenerative diseases. While much research has focused on age-related changes in post-mitotic cells e.g., neurons, little is known about the effects of aging on the structure and function of the urothelial cells that line the lumen of the urinary bladder.

**Methods:** Analyzed by morphometric analysis and stereology urinary bladders taken from young rats (~3-4 months), adult rats (~12 months), and aged rats (~24-30 months old) to assess age-related changes in the urotheliumProtease activity assays of urothelial cell lysatesWestern blot analysis of proteins involved in autophagy

**Results:** The urothelium of aged rats possessed many unusually large (up to 5µm in diameter) endolysosomes that contained numerous intraluminal vesicles of various size, shape, and electron density. Undigested cellular debris including membrane were often observed inside these structures suggesting that these organelles lack the ability to effectively process and/or remove unwanted cellular material via either dysfunctional lysosomal degradation or autophagy. Morphometric analysis showed that the fractional volume of endolysosomes (relative to total cell volume) from aged urothelium was nearly four-fold greater than that of young rats with no increase in total cell volume. Interestingly, no age-related changes in volume were observed among other organelles in the degradative pathway including multivesicular bodies and terminal lysosomes. Consistent with dysregulated degradation, cell lysates from aged urothelium showed a greater than three-fold decrease in cathepsin B protease activity. Finally, total cellular levels of the autophagic protein marker, LC3, in aged urothelium were undetectable by Western blot suggesting a defect in processing of intra-cellular material by autophagy.

**Conclusion:** Our findings suggest that age-related changes in urothelium result in lysosomal and/or autophagic processing of material and may provide insight into general mechanisms of aging throughout the body.
**51-A Poster:** Effect of Myocardial Infarction on Insulin Resistance: Role of Macrophage Subsets

**Presenter:** Sathish Vasamsetti, Post-Doctoral Fellow  
Vascular Medicine Institute

**Research Interest:** Bench

**Mentors:** Partha Dutta PhD

**Funding Source:** NHLBI  
(4R00HL12076-03)

**Authors:** Sathish Vasamsetti PhD, Jonathan Florentin PhD, Emillie Coppin PhD, Partha Dutta PhD

**Introduction:** Myocardial infarction (MI) is the leading cause of cardiac associated mortalities in the USA. Although most of the patients with MI survive the immediate acute event, the long term mortality is still high. Non-diabetic patients after MI develop insulin resistance (IR). Recent clinical reports showed IR has direct proatherogenic effect at the level of atherosclerotic plaques leading to a series of cellular atherogenic events and plaque progression. But the mechanistic underpinnings of IR after MI are poorly explored.

**Methods:** We found that 50% of non-diabetic patients (fasting blood glucose levels 99±2.5 mg/dl) develop hyperglycemia (fasting blood glucose levels 141±13 mg/dl) after MI, suggesting IR following MI. To investigate the mechanisms behind IR after MI, we performed coronary ligation in: a) non-diabetic lean wild type mice b) obese mice with insulin resistance. We tested insulin sensitivity with an intraperitoneal glucose tolerance test.

**Results:** We found that the mice with coronary ligation had higher insulin resistance on day 7 and 28 after MI. This was in line with higher serum insulin levels and lower glycogen contents in the liver after MI. We did not find any alteration in serum cortisol and catecholamine levels, known to induce IR, on day 7 and 28 after MI. Additionally, lipolysis after MI was unchanged. We found there was a significant increase in monocyte-derived inflammatory CX3CR1+ CCR2+ macrophages in visceral adipose tissue (VAT) in mice and humans with MI. Concomitantly, the number of CX3CR1- CCR2- VAT resident macrophages decreased after MI. Congruently, our data revealed that the levels of macrophage colony stimulating factor (M-CSF), a cytokine required for tissue resident macrophage survival, diminished after MI. M-CSF supplementation in mice with MI improved IR and decreased inflammatory phenotype of VAT macrophages, suggesting the role of M-CSF in reducing inflammation and maintaining insulin sensitivity. In line with this, we found that M-CSF-deficient mice had insulin resistance.

**Conclusion:** Here we show that MI induced myelopoiesis promotes infiltration and accumulation of inflammatory CX3CR1+ CCR2+ macrophages in VAT. Concomitantly, the loss of tissue resident anti-inflammatory CX3CR1- CCR2- VAT macrophages due to loss of M-CSF causes insulin resistance.
**52-A Poster:** Palmitoylation of the Epithelial Na+ Channel affects regulation by bile acids

**Presenter:** Xue-Ping Wang, Post-Doctoral Fellow  
Renal-Electrolyte  

**Research Interest:** Bench  

**Mentors:** Ossama B. Kashlan PhD  

**Funding Source:** R01  

**Authors:** Xue-Ping Wang PhD, Ossama B. Kashlan PhD

**Introduction:** The epithelial Na+ channel (ENaC) is a member of the ENaC/Degenerin family of ion channels, which are characterized by a trimeric composition with a large extracellular domain, two transmembrane helices and cytoplasmic N and C termini. ENaC is mainly found at the apical surface of Na+-transporting epithelia, such as the distal nephron of the kidney, distal colon, and lung alveoli and airway. There, ENaC plays a critical role in maintaining Na+ homeostasis, blood pressure, and airway surface liquid height. ENaC is assembled from three homologous subunits (alpha, beta and gamma) and its activity is modulated by several post-translational modifications, including palmitoylation. Two cytoplasmic cysteine residues each in the beta subunit (Cys-43 and Cys-557) and the gamma subunit (Cys-33 and Cys-41) subunit are palmitoylated. Palmitoylation at these sites activate the channel, likely through increasing membrane association of intracellular channel structures. Bile acids have recently been reported to activate ENaC.

**Methods:** We hypothesized that palmitoylation affects ENaC’s response to bile acids. We tested this by removing palmitoylation sites using site-directed mutagenesis, and then using electrophysiology to examine the effect of mutation on channel activation by bile acids.

**Results:** In this study, we found that removing palmitoylation sites strongly potentiated deoxycholic acid stimulation of ENaC currents. When we examined each of the sites individually, we found that only sites in the N-terminal cytoplasmic domains had an effect. We also hypothesized that ENaC mechanosensitivity is sensitive to channel palmitoylation. We found that removing palmitoylation sites increased ENaC’s response to laminar shear stress.

**Conclusion:** The palmitoylation sites are in proximity to the transmembrane domains of the channel. We propose that palmitoylation of the beta and gamma subunits regulates channel activity by modulating the channel’s response to membrane composition and mechanical stress.
**53-A Poster:** Increasing Endothelial Permeability with Ultrasound and Microbubbles for Therapeutic Delivery Applications

**Presenter:** Daniel Whitehurst, Medical Student  
**Cardiology**

**Research Interest:** Bench Cardiology

**Mentors:** Flordeliza Villanueva MD

**Funding Source:** Center for Molecular Imaging and Therapeutics

**Authors:** Daniel Whitehurst BS, Darwin Kwok BS, Brandon Helfield PhD, Xucai Chen PhD, Flordeliza Villanueva MD

**Introduction:** Intravascular, therapeutic-loaded microbubbles (MBs) can be targeted to release their payload with ultrasound (US) at disease sites, such as the delivery of antimiR-23a to treat left ventricular hypertrophy. Despite initial success in pre-clinical models, the mechanisms by which this intravascular approach delivers payloads to extravascular tissue remains unknown. We hypothesize that US and MB treatment increases endothelial permeability without causing extensive endothelial layer damage, allowing therapeutics to diffuse from the blood vessel into the extravascular tissue.

**Methods:** Human umbilical vein endothelial cells (HUVECs) were seeded and grown to confluency on the basal side of transwell membranes to create a model endothelial layer. MBs at either a 3:1 or 10:1 MB:cell ratio were injected into the lower chamber before exposure to various 1 MHz pulsed US conditions (50 to 400 kPa, 5 to 100 µs pulse duration and 1 to 1000 ms pulse interval) for 10 seconds. To quantify endothelial layer damage, cell number (Hoechst) and surface area coverage (membrane stain CellMask) were measured with fluorescence microscopy (20x) pre-US treatment to assess baseline levels. After treatment, transwells were re-imaged to measure cell number, surface area coverage and cell viability (calcein-AM). Calcein positive cells were defined as viable. To quantify increases in endothelial permeability, MBs and FITC labeled dextran (10 kDa) were added to the lower chamber of the transwell pre-treatment, and the concentration of the FITC dextran in the upper chamber was measured at 0, 15, 30, 45, 60 and 120 minutes after treatment using a microplate photometer (485 nm/535 nm). HUVEC seeded transwells receiving no US served as a control.

**Results:** Initial experiments using US conditions developed in vitro to maximize drug delivery (10:1 MB:cell ratio, 250 kPa, 100 µs pulse duration and 1 ms pulse interval) displayed a 568±93% increase in diffusion compared to control at 60 min (n=3), but with an unacceptable 31±7% cell viability (n=2). At milder US conditions (3:1 MB:cell ratio, 125 kPa, 10 µs pulse duration and 10 ms pulse interval) a still significant 40±28% increase in diffusion was measured compared to control at 120 minutes (p<0.001; n=8) while maintaining 89±1% viability (n=5), 1±4% cell loss (n=6), and 5±1% coverage loss (n=4).

**Conclusion:** US and MB treatment successfully increased the diffusion of a surrogate therapeutic across an endothelial layer while maintaining cell viability, thus demonstrating a mechanism by which US and MB treatment could facilitate the passage of a therapeutic to extravascular disease sites.
**Poster Abstracts**

**54-A Poster:** Targeting GFI1 reduces osteoclastogenesis and bone resorption through integrin-dependent cytoskeleton dynamics

**Presenter:** Peng Zhang, Post-Doctoral Fellow  
Hematology/Oncology

**Research Interest:** Bench

**Mentors:** Deborah L. Galson PhD

**Funding Source:** R01

**Authors:** Peng Zhang PhD, Quanhong Sun PhD, Juraj Adamik PhD, ROng Chong PhD, Konstantinos Verdelis PhD, Deborah L. Galson PhD

**Introduction:** Multiple myeloma (MM), the most frequent cancer to involve bone, enhances osteoclast formation and suppresses new bone formation. The MM-induced bone destruction significantly contributes to patient morbidity and mortality. We reported that MM induces Growth Factor Independent-1 (GFI1), a transcription repressor, in bone marrow stromal cells, which recruits repressive epigenetic modifiers to the Runx2 gene, a key osteoblast differentiation factor. Importantly, GFI1 knockdown after MM exposure reversed the osteoblast differentiation blockade. These data suggest that targeting GFI1 might be a therapeutic approach to repair MM-induced bone lesions. Therefore, to understand the consequence of targeting GFI1 in myelomatous bone, we investigated GFI1 function in osteoclasts.

**Methods:** Analyses of bones from WT and Gfi1-/- mice by microCT, flow cytometry, and immunohistochemical staining. Osteoclast formation assays from WT and Gfi1-KO mouse bone marrow monocytes (BMM) and from the pre-osteoclast cell line RAW264.7 transduced with SCR vs shGfi1 were analyzed by TRAP assays, fluorescence confocal microscopy, time-lapse imaging. Expression of GFI1 and a set of osteoclast marker genes during osteoclast differentiation were evaluated by real-time quantitative PCR and western blot or immunostaining. MM1.S cell-conditioned media (72 h) was added (1/100) to some cultures.

**Results:** Gfi1 mRNA is upregulated during osteoclast differentiation, and BMM exposure to MM-conditioned media enhanced Gfi1 expression and increased osteoclast size. Gfi1-KO 8w-old mice show a mildly increased bone volume reflecting a decrease in bone resorption in spite of significantly increased OCL numbers. BMM from Gfi1-KO mice contained increased numbers of osteoclast progenitors, but Gfi1-KO BMM formed smaller osteoclasts that were less spread. Similarly, shGfi1-RAW264.7 cells formed smaller, less spread osteoclasts. Further, Gfi1-KO osteoclasts formed fewer and shorter resorption tracks on bone slices with less overall resorption, suggesting that GFI1 is required for osteoclast function. There was a progressive rescue of GFI1-deficient osteoclast formation with increasing initial plating density, suggesting that lack of GFI1 impairs osteoclast migration. Moreover, time-lapse imaging of osteoclast formation confirmed that GFI1-deficiency impaired osteoclast migration. In the absence of GFI1, there was reduced integrin β3 and p130Cas expression, cytoskeletal disorganization, reduced pseudopodia formation, and lack of acid vacuole release, together resulting in decreased resorption.

**Conclusion:** Our study has made the novel finding that GFI1 has an important role in osteoclastogenesis; GFI1 is required for correct regulation of actin dynamics controlling osteoclast migration and resorption. Therefore, targeting GFI1 should both increase bone formation and decrease bone resorption, which could generate new therapeutic approaches for cancer-induced bone disease.
55-A Poster: Poor Agreement between Transthoracic Echocardiography and Right Heart Catheterization for Assessment of Pulmonary Hypertension Severity - Clinical Applications in the TAVR Era

Presenter: Islam Abdelkarim, Post-Doctoral Fellow
Research Interest: Clinical Cardiology

Mentors: Joao Cavalcante MD
Funding Source: None

Authors: Islam Abdelkarim MD, Jeffrey Xu MD, Michael Sharbaugh MPH, Andrew Althouse PhD, William Katz MD, Frederick Crock MD, Matthew Harrinstein MD, Dustin Kliner MD, Forozan Navid MD, Joon Lee MD, John Schindler MD, Thomas Gleason MD, Joao Cavalcante MD

Introduction: Pulmonary hypertension (PH) is common and prognostically important in patients undergoing transcatheter aortic valve replacement (TAVR). However, the accuracy of PH severity assessment by transthoracic echocardiogram (TTE) when compared to gold standard right heart catheterization (RHC) is currently unknown in these patients.

Methods: Patients being evaluated for TAVR who underwent TTE and RHC within 3 days. PH severity was classified as none, mild, moderate, and severe using the following PASP cutoffs: <35, 35-45, 46-59 and = 60 mmHg, respectively. Weighted ? statistics evaluated PH severity agreement. Bland-Altman plots and linear regression correlated PASP between 2 methods.

Results: 86 patients with severe AS were identified. Mean age 84±6 years, indexed AV area=0.33±0.1 cm²/m², LVEF=51±15%, PASP=45±20 mmHg. Although linear correlation of PASP between RHC and TTE was modest (r=0.64, p <0.001, Panel A), PH severity agreement was poor (?=0.34, Panel B). Out of 51/86 patients with no/mild PH by TTE, 25/51 (49%) were reclassified to >= moderate PH by RHC with 10/51 (20%) as severe PH by RHC. TTE was very specific for severe PH screening (0.96, 95% CI 0.87-0.99) but not adequately sensitive (0.47, 95% CI 0.29-0.65).

Conclusion: Modest agreement exists between TTE vs. RHC for PH severity assessment with 1/5 patients reclassified to severe PH by RHC. Accurate PH assessment is critically important and RHC performance should be considered in adjunction to coronary angiography in TAVR patients.
**56-A Poster:** The Deleterious Effects of Atrial Fibrillation in Heart Failure: Insights Using Impedance Cardiography

**Presenter:** Mohammad Alhamaydeh, Post-Doctoral Fellow  
**Research Interest:** Clinical Cardiology

**Mentors:** Imad Alghoulah PhD  
**Funding Source:** Memorial University of Newfoundland, Canada

**Authors:** Mohammad Alhamaydeh MD, Salah Alzaiti PhD, Fadi Kharim PhD

**Introduction:** Heart failure (HF) affects nearly 23 million individuals worldwide, including 5.1 million individuals in the United States. HF and atrial fibrillation (AFIB) often co-exist. Each is considered both a cause and consequence of the other, leading to more derangements of systolic and diastolic functions of the left ventricle that are not present in normal sinus rhythm. Hemodynamic monitoring typically requires invasive monitoring and is typically performed in inpatient settings. We sought to evaluate the clinical utility of impedance cardiography, as a novel non-invasive tool for hemodynamic monitoring, to characterize the electromechanical events seen in ambulatory, optimally-managed HF patients with and without AFIB.

**Methods:** This was an observational study that recruited ambulatory patients from an outpatient heart failure clinic. Patients with NYHA heart failure class I-III were eligible. There were no restrictions to age, sex, or ejection fraction. In supine resting position, consented patients underwent non-invasive 12-lead ECG and hemodynamic monitoring using BioZ Dx Impedance Cardiography (Sonosite Inc., WA, USA). Impedance cardiography is a non-invasive technique to record cardiac hemodynamic functions in real-time, including parameters of cardiac output, contractility, and systemic resistance. ECGs were evaluated by a reviewer blinded to clinical data. Participants with pacing (n=12) or left bundle branch block (n=9) were excluded. Effect sizes (ES) were estimated using Pearson’s r coefficient and groups were compared using independent samples t-test. Significance was set at p<0.05 two-tailed.

**Results:** The final sample (n=32) was 62±14 years of age and 66% male with ejection fraction of 33±13%. Compared to those with normal sinus rhythm (n=23, 72%), those with AFIB (n=9, 28%) had significantly lower stroke volume, lower left stoke work index, higher systemic stroke resistance index, and lower total arterial compliance. These parameters were also mediators through which AFIB impaired cardiac output, with the greatest effect size observed through altering systemic stroke resistance index (ES= –0.30), a measure of afterload on a per beat basis.

**Conclusion:** Our results suggest that there are multiple pathways through which AFIB negatively affects cardiac output in HF. The fact that increased afterload constitutes one of these pathways is intriguing and requires further research. Overall, impedance cardiography is a safe and effective tool that can be used in HF patients to characterize the unique electromechanical events and their systemic cardiovascular effects seen in those with AFIB vs. those without.
57-A Poster: Establishment of a Volunteer Stool Donor Bank for Fecal Microbiota Transplantation

Presenter: Tatiana Bogdanovich, Junior Faculty Infectious Diseases

Research Interest: Clinical

Mentors: None

Funding Source: UPMC

Authors: Tatiana Bogdanovich MD, Scott Curry MD, Yohei Doi MD, Nicolas Sluis-Cremer PhD, David Binion MD, Marc Schwartz MD

Introduction: Fecal microbiota transplant (FMT) is an effective therapy for recurrent Clostridium difficile infections (rCDI) which failed to respond to prolonged antibiotic treatment. At UPMC, 19 FMT procedures were performed between 12/2014-04/2016, with an 89% clinical success rate, using recipient-directed donors. The disadvantages of this approach included: (i) difficulty and stress associated with identifying a suitable donor; (ii) out-of-pocket costs for recipients; and (iii) prolonged wait times for the FMT procedure. Accordingly, we established a Volunteer Stool Donor (VSD) bank to provide on-demand, safe FMT doses from carefully selected donors.

Methods: Since 04/2016 we are actively recruiting elite, healthy VSDs who are >18 years of age, have normal body weight (BMI, 18.5-24.9), have no chronic medical conditions that require prescription medication, and have no history of travel outside the US/Canada in the last 12 months. All prospective donors are screened using an extensive on-line questionnaire, after which the qualified donors are asked to submit stool samples. Following a 2 week quarantine period, the VSD then undergoes a free physical examination and extensive testing (including blood and stool) to exclude the potential transmission of infectious agents, and to prevent mismatches between donor and recipients for latent viruses that undergo fecal shedding.

Results: Seven of 34 potential donors met the VSD screening criteria and completed the stool donation process. One VSD was found to be an asymptomatic C. difficile carrier and was subsequently removed from the VSD bank. The remaining six VSDs had a median age of 32 (range, 25-50) and 67% of them were female. Seropositivity to CMV, EBV, HHV6, HSV-1, HSV-2 and JC virus was 17%, 68%, 100%, 33%, 0%, and 68%, respectively. A total of 6 patients with rCDI have received FMT using VSD doses by colonoscopy (1), enteroscopy (1) or freeze-dried capsules (4). The interim clinical response rate is 100% (the primary outcome for FMT is the absence of any diarrhea occurrence and/or a positive C. difficile stool test = 12 weeks). Two serious adverse events occurred: one recipient experienced abdominal pain/constipation (possibly related to FMT) while a second recipient experienced cholangitis related to a biliary duct obstruction (unlikely related to FMT); both conditions subsequently resolved.

Conclusion: The creation of a VSD bank allows for safer and more timely FMT therapy for patients with rCDI. The interim clinical success rate is 100%.
**58-A Poster:** Prognostic Value of Right Ventricle-Pulmonary Artery Coupling in TAVR Patients - Time to Integrate the Right Side Unit

**Presenter:** Joao Cavalcante, Junior Faculty Cardiology  
**Research Interest:** Clinical

**Mentors:** None  
**Funding Source:** None

**Authors:** Islam Abdelkarim MD, Michael Sharbaugh PhD, Andrew Althouse PhD, Jeffrey Xu MD, Wei Han MD, William Katz MD, Frederick Crock MD, Matthew Harinstein MD, Dustin Kliner MD, Forozan Navid MD, Joon S Lee MD, John Schindler MD, Thomas Gleason MD

**Introduction:** Right ventricular (RV) function and pulmonary hypertension (PH) are prognostically important in patients receiving transcatheter aortic valve replacement (TAVR). We hypothesized that the ratio between tricuspid annular plane systolic excursion (TAPSE)-pulmonary artery systolic pressure (PASP) would assess the RV-arterial coupling and would have superior prognostic value than either parameter alone.

**Methods:** Consecutive TAVR patients from 07/2011 through 01/2016 with comprehensive echocardiogram at baseline. TAPSE/PASP quartiles were tested for the prediction of all-cause mortality. Cox regression and Kaplan-Meier analyses with TAPSE and PASP and then combined as the ratio were performed. Akaike information criterion (AIC) compared relative quality of the prediction models.

**Results:** A total of 457 patients [age 84 years, LVEF 54 ± 13%, PASP 44 ± 17 mmHg] were included. TAPSE/PASP quartiles showed a dose-response relationship with survival (Figure). This remained significant (HR for lowest quartile vs. highest quartile=2.32, 95% CI 1.16-4.64, p=0.02) after adjusting for age, LVEF, and STS-PROM. Comparison of model AIC statistics showed that the TAPSE/PASP ratio was a better predictor than either measurement by itself.

**Conclusion:** Assessment of the RV-pulmonary artery coupling as the TAPSE/PASP ratio predicts all-cause mortality in TAVR patients. Incorporation of right-side unit into the risk stratification might provide strategies to further improve TAVR outcomes.
59-A Poster: Gastric Electrical Stimulator for Gastroparesis

Presenter: Anwar Dudekula, Junior Faculty General Internal Medicine
Research Interest: Clinical

Mentors: Klaus Bielefeldt MD, David Levinthal MD
Funding Source: None

Authors: Anwar Dudekula MD, David Levinthal MD, Klaus Bielefeldt MD

**Introduction:** Gastric Electrical stimulation (GES) has emerged as a new potential therapeutic option in patients with medically refractory gastroparesis (GP). However, improvement in gastric motility may not improve associated symptoms, and these patients may continue to have high health care utilization after placement of GES. We assessed the long term efficacy of GES utilizing Nationwide Inpatient Sample (NIS) and the state data for California (CA) and Florida (FL), and tested our hypothesis that surgical rates are increasing, associated with considerable morbidity and limited impact on healthcare resource utilization.

**Methods:** Index hospitalizations were defined by the primary diagnosis of gastroparesis associated with the procedural code for neural stimulator after exclusion of potential confounding disorders such as underlying malignancy. Age, sex, ethnic background, insurance coverage, comorbidities and complications during the hospitalization were captured. Resource utilization, defined by emergency room (ER) visits or admissions were captured for periods before and after insertion of the GES using data for CA and FL. A fixed effects regression model was used to assess health care utilization before and after GES placement adjusting for all non-time-varying confounders in per-person pre-post comparison.

**Results:** Between 2004 and 2013, the proportion of GP patients with GES rose from 0.03% (in 2001) to 0.22% (in 2011) (p=0.003). Most of the patients are female (76%), white (60%), and have a low perioperative risk as defined by an age around 40 years and limited comorbidities. Consistent with the known patient profile for functional diseases, mood disorders commonly coexist (22%). Perioperative complications arose in 13% during the index hospitalization. A longitudinal analysis based on the CA and FL data showed ER visits and readmission rates of 30% and 99%, respectively, within 30 days after the index hospitalization. Resource utilization could be tracked for 319 patients for a median time of 1057 days (IQR 581-1598) before and 669 days (IQR 247-1063) after GES insertion. The fixed effects regression analysis showed that there is no statistically significant association between GES placement and health care utilization before and after GES (p=0.935).

**Conclusion:** Using a very conservative approach, we determined that GES for GP are rising and account for at least 0.4% of gastroparesis patients. Despite a relatively young patient population, perioperative complication and 30-day readmission rates are high, demonstrating a significant morbidity. In contrast, the persistently high resource utilization suggests a limited benefit, which should prompt us to question the utility of surgery in functional illnesses, such as gastroparesis.
**Introduction:** Aneurysmal subarachnoid hemorrhage (SAH) is associated with significant mortality and disability. Neuro-cardiac injury may exist in SAH, but is poorly understood. The aim was to test the hypothesis that global longitudinal strain (GLS) can detect neuro-cardiac injury and is associated with in-hospital mortality.

**Methods:** We studied 255 patients with acute SAH (0-5 days from bleed) in the SAHMII study (R01NR04221). Routine biplane ejection fraction (EF) and speckle tracking GLS from 3 apical views were assessed. Peak troponin values were determined and clinical SAH severity was classified by Hunt-Hess grade. In-hospital mortality was tracked.

**Results:** GLS was feasible in 228 (89%) of SAH patients (73% were female). There were 57 (25%) patients with abnormal GLS (defined as >-17%). Abnormal and normal GLS groups had similar age (53± 11 vs. 52± 10 yrs, P = 0.66) and gender (female 77% vs. 70%, P = 0.30). Abnormal GLS was associated with significantly higher troponin levels [0.71 (0.1 - 3.5) vs. 0.1 (0.09 - 0.26), P < 0.001], and lower EF (53.2 ± 12.1% vs. 64.4 ± 5.7%, P < 0.001). Abnormal GLS was also associated with greater severity of SAH (Hunt-Hess grade, P = 0.01). In-hospital mortality was 9% (20 patients) in total and 18% (10 patients) in the patients with abnormal GLS. Abnormal GLS was significantly associated with in-hospital mortality overall (OR 4.4, 95% CI 1.72 - 11.3, P = 0.002), while EF was not (OR 0.97, 95% CI 0.93 - 1.01, P = 0.175). In particular, abnormal GLS was associated with in-hospital mortality in patients with preserved EF > 50% (HR 5.41, 95% CI 1.78 - 16.4, P = 0.003) even after adjusting for the severity of SAH.

**Conclusion:** Neuro-cardiac injury may be detected by GLS in patients with acute SAH. Abnormal GLS was significantly associated with greater clinical severity of SAH and higher troponin levels. Importantly, abnormal GLS was associated with in-hospital mortality, even in patients with preserved EF and has clinical prognostic utility for SAH.
**Introduction:** The value of serum bone turnover markers for predicting changes in bone mineral density (BMD) and microarchitecture after osteoporosis treatment is largely unstudied in frail, elderly women. Such patients have the highest fracture morbidity and mortality and need targeted therapy. Unlike healthy participants in pivotal bisphosphonate trials, sedentary long-term care residents have multiple comorbid conditions that may impact bone turnover. We performed secondary analysis of a zoledronic acid trial in elderly women residing in long-term care to determine if early changes in bone turnover predicted longer-term changes in BMD and a novel microarchitecture assessment.

**Methods:** Data from 145 women (mean age 86.9) were included. Serum C-terminal telopeptide (s-CTX), a marker of bone resorption, and serum procollagen type-1 N-terminal propeptide (P1NP), a marker of bone formation, were assessed at baseline and 6 months. BMD was measured at baseline, 12, and 24 months at the lumbar spine and hip by dual-energy x-ray absorptiometry (DXA). Trabecular bone score (TBS), a measure of bone microstructure, was determined from lumbar spine DXA. Bone marker changes were categorized into tertiles. Linear mixed models were used to determine associations between marker change and the percent change of BMD or TBS at 12 and 24 months.

**Results:** A 0.1 nmol/L BCE 6-month decrease in s-CTX was associated with increased total hip (0.55%, p<0.03) and femoral neck BMD (0.84%, p<0.01) at 12-months and with a deceased (structurally worse) TBS score (-0.77%, p<0.04) at 24 months. P1NP increases of 10 pg/ul were associated with BMD improvements at the lumbar spine (0.47% at 12- and 0.69% at 24-months, both p<0.03), total hip (0.72% at 12- and 0.71% at 24-months, both p<0.01), and femoral neck (1.1% at 12- and 1.0% at 24-months, both p<0.01). Women in the lowest tertile with an early decrease in s-CTX greater than 39% had a 2.1-2.8% greater increase in lumbar spine BMD at 24 months (p<0.04) and a 2.1-2.6% greater increase in total hip BMD at 12- (p<0.03) and 2.6-3.3% at 24-months (p<0.01) compared to the other tertiles. Those in the lowest tertile of P1NP early change (<-37%) had 2.4-3.9% and 2.3-3.2% greater increases in spine and total hip BMD, respectively, compared to those in the higher tertile (>0%). Bone markers had minimal association with changes in TBS microstructure.

**Conclusion:** Early bone turnover changes in frail, elderly women with osteoporosis are associated with long-term changes in lumbar spine and total hip BMD but not microstructure.
**62-A Poster:** Fracture liaison service in an open health care system and changes in post-fracture management

**Presenter:** Mary Kotlarczyk, Post-Doctoral Fellow
**Research Interest:** Clinical Geriatric Medicine

**Mentors:** Susan Greenspan MD
**Funding Source:** T32

**Authors:** Mary Kotlarczyk PhD, Karen Vujevich MSN, CRNP, Subashan Perera PhD, Susan Greenspan MD

**Introduction:** Secondary fracture prevention is lacking in patients who sustain an acute fragility fracture, despite several quality improvement guidelines and the availability of bone density testing and medications to reduce future fracture risk. The Fracture Liaison Service (FLS) model of care has been effective in narrowing the care gap between acute fracture repair and osteoporosis management. Most research demonstrates the establishment of FLS models in closed systems where hospitals, providers, payers, and patients have closely aligned incentives. We describe pre- to post-implementation of an FLS at UPMC Montefiore and Presbyterian hospitals to improve care in an open health care system with nonaligned incentives.

**Methods:** Candidate patients were men and women age 50+ who were hospitalized with a fragility fracture. Assessments included quality metrics such as serum 25-hydroxyvitamin D, bone density testing, and initiation of osteoporosis therapy if needed within 6 months after the fracture. Data was extracted from the electronic medical records of 100 fracture patients seen prior to establishment of the FLS to establish a baseline. After FLS implementation, a nurse practitioner coordinated patient care and follow-up including assessment, treatment, and education about bone health. Pre- and post-FLS outcomes were compared using a t-test or Fisher’s exact test.

**Results:** FLS care was initiated in 247 inpatients. Bone density testing rates improved from 9% pre-FLS to 57.1% post-FLS (p<0.001). Vitamin D assessment also increased from 20% pre-FLS to 92.2% post-FLS (p<0.001). Patients receiving appropriate pharmacologic therapy increased from 4% pre-FLS to 44.5% with FLS (p<0.001). The number of patients who received appropriate BMD testing and/or pharmacologic therapy intervention improved from only 10 patients pre-FLS (10%) to 147 patients post-FLS (59.5%, p<0.001).

**Conclusion:** The FLS model of care improves compliance with national quality improvement metrics and can be implemented in an open health care setting such as UPMC to improve assessment and treatment of osteoporosis in patients with fragility fractures.
**Poster Abstracts**

**63-A Poster:** Are Acute Kidney Injury Biomarkers Expressed in Glomeruli of Lupus Nephritis Biopsies?

**Presenter:** Kelly Liang, Junior Faculty

**Research Interest:** Clinical Renal-Electrolyte

**Mentors:** Paul Palevsky MD, John Kellum MD

**Funding Source:** K23

**Authors:** Kelly Liang MD, David Emlet PhD, Sheldon Bastacky MD, Paul Palevsky MD, John Kellum MD

**Introduction:** Acute kidney injury (AKI) biomarkers, including urine insulin-like growth factor-binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinases-2 (TIMP-2), and kidney injury molecule 1 (KIM-1) have been well validated in heterogeneous critically ill populations as markers of tubular injury and cell-cycle arrest. However, they have not been studied extensively in glomerular diseases such as lupus nephritis (LN), and their utility as markers of glomerular injury has been suggested but remains unknown. In LN, early diagnosis is paramount to guide therapy with immunosuppression to prevent renal failure. Preliminary studies in animal models of LN suggest that AKI biomarkers may play a pathophysiologic role in LN. These studies have shown that urinary and/or kidney expression of KIM-1 and TIMP-2 are associated with LN activity in mice and humans, but no major studies have been reported on IGFBP7 in LN. Therefore, we sought to determine whether IGFBP7, TIMP-2, and KIM-1 are expressed in human renal tissues of LN, in order to provide background for further studies of these urine and serum AKI biomarkers in LN patients.

**Methods:** Five frozen renal biopsy samples with a confirmed diagnosis of LN class IV were identified using an electronic database from the Renal Pathology Department of University of Pittsburgh. Controls were human renal tissue from kidneys rejected for renal transplant. The samples were subjected to standard double-label indirect immunofluorescence with antibodies to IGFBP7, TIMP-2, and KIM-1 and appropriate fluorochrome-conjugated secondary antibodies. In vivo expression of biomarkers were determined semi-quantitatively using confocal microscopy.

**Results:** While the level of expression was variable from sample to sample, in every case, the levels of expression of IGFBP7, TIMP2, and KIM-1 were greater in the glomeruli of the LN biopsies compared to control kidney tissue (non-LN control and negative control samples).

**Conclusion:** This is the first study to evaluate glomerular expression of TIMP-2 and IGFBP7 in glomeruli of patients with LN. These preliminary results show the AKI biomarkers IGFBP7, TIMP2, and KIM-1 expression was greater in the glomeruli of the LN biopsies compared to control kidney tissues, suggesting they may either play a pathophysiologic role or be a marker for acute kidney injury in LN. Therefore, further studies are warranted to determine if they may be useful biomarkers in LN and other glomerular disorders.
64-A Poster: Pilot Study of Microbubble Contrast-Enhanced Vascular Ultrasonography: A Novel Method of Detecting Large Vessel Vasculitis?

Presenter: Kimberly Liang, Junior Faculty
Rheumatology and Clinical Immunology

Research Interest: Clinical

Mentors: Larry Moreland MD
Douglas Landsittel PhD

Funding Source: Vasculitis
Foundation

Authors: Kimberly Liang MD, Douglas Landsittel PhD, Bernadette Sendon BS, Donald Jones MS, Suresh Mulukutla MD, Steven Reis MD, Ali Hakim Shoushtari MD, Larry Moreland MD

Introduction: A key unmet need in the monitoring of disease activity in large vessel vasculitides (LVV), i.e., giant cell arteritis (GCA) and Takayasu arteritis (TAK), is the ability to differentiate active vasculitic disease activity from atherosclerotic damage through the use of noninvasive imaging modalities. In LVV, the inflammatory process begins at the vasa vasorum in the adventitia, with vasa vasoritis. Thickened adventitia and medial fibrosis are key features that differentiate vasculitis from atherosclerosis. A novel imaging modality that can noninvasively detect increased neovascularization and thickening in large vessels’ adventitia is microbubble contrast-enhanced carotid ultrasonography (CU). In studies using CU, higher densities of vasa vasorum correlated with plaque vulnerability and atherosclerosis progression. Our objective was to establish feasibility of measuring adventitial vasa vasorum density (aVVD) in LVV patients; to compare aVVD in clinically active vs. inactive LVV patients; and to examine various serum vascular and inflammatory biomarkers in these patients.

Methods: We performed a preliminary analysis of an ongoing cross-sectional study of 7 LVV patients (2 active, 5 inactive) to illustrate feasibility of the novel CU technique. All subjects met ACR criteria for GCA or TAK. All subjects underwent CU with measurement of carotid intima-media thickness (cIMT, using maximum of both sides) and mean common carotid artery (CCA) adventitial to lumen videointensity ratio (using maximum of both sides) to quantify aVVD. Data on demographics and disease characteristics were collected on all subjects. Serum biomarkers of CD40L, matrix metalloproteinase-9, myeloperoxidase, E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 were measured in all subjects by enzyme-linked immunosorbent assay (ELISA). The inflammatory markers high sensitivity C-reactive protein and erythrocyte sedimentation rate were also measured in all patients.

Results: Seven subjects (4 TAK and 3 GCA) were recruited; 2 had active and 5 had inactive disease. The mean cIMT of the two active LVV subjects was 1.23 mm, and the mean cIMT of four inactive subjects was 0.91 mm. The maximal aVVD of the CCA’s far wall for the two active LVV subjects was 0.58, versus 0.50 for the five inactive LVV subjects. Wide variation in serum biomarker levels were seen in the inactive subgroup, and statistical testing between active vs. inactive will be performed when the study of n=20 participants is completed.

Conclusion: Measurement of aVVD in LVV patients is feasible utilizing the novel CU technique. In this pilot study, the aVVD was slightly higher in active vs. inactive subjects. Our study is ongoing, with plans for targeted enrollment of larger numbers and comparison with control (non-LVV) subjects.
**Introduction:** Background: Given the complexities and risks of allogeneic HCT, patients and their family caregivers may experience elevated psychological distress, including symptoms of anxiety and depression, in anticipation of the procedure. Patients and caregivers also bring with them their pre-HCT experiences of diagnosis, prior treatment, and associated burdens, thus potentially compounding their acute distress. Identification of clinical, psychosocial, and sociodemographic factors related to pre-HCT distress would allow targeting of patients and caregivers who may require assistance during the HCT process.

**Methods:** Method: Consecutive patients (n=111, 56 men; mean age 53.7 (SD 10.3); 95% white) and their caregivers (n=110, 29 men; mean age 53.2 (SD 13.6); 95% white) separately completed questionnaires in the week before HCT. Questionnaires included the Hospital Anxiety and Depression Scale, the Cancer and Treatment Distress Scale (patient or caregiver version as appropriate), perceived threat, perceived control, self-efficacy, relationship quality via the modified Dyadic Adjustment Scale, and physical quality of life (SF36 Physical composite). Multivariate linear regression analysis was used to identify factors potentially associated with patient and caregiver anxiety or depression, including disease type, donor type, and patient and caregiver sociodemographic and psychosocial factors.

**Results:** Results: Family caregivers had higher levels of anxiety and depression symptoms than patients, t(106) = -3.653; p < .001 and t(106) = -2.717; p < .01 respectively. Thirty percent of caregivers vs. 17% of patients met criteria for moderate-severe anxiety and a lesser amount (5% for both) met criteria for moderate-severe depression. Caregivers reported greater perceived disease threat and lower relationship quality than patients. Multiple regressions revealed that patient anxiety was related to younger age (b = -.211, p = .005) and greater cancer-related distress (b = .589, p < .001), while caregiver anxiety was related to lower self-efficacy (b = -.194, p = .011) and greater cancer-related distress (b = .551, p < .001). Similarly, patient depression was related to lower perceived control (b = - .166, p = .050), greater cancer-related distress (b = .290, p = .005), and lower physical functioning (b = -.229, p = .008), while caregiver depression was related to greater cancer-related distress (b = .423, p < .001). Disease type and donor type were not related to anxiety and depression.

**Conclusion:** Conclusion: Family caregivers may be more emotionally vulnerable than patients before HCT and in need of additional assistance. Cancer-related distress was the strongest correlate of anxiety and depression in both patients and caregivers, suggesting that distress related to their cancer experience and its consequences plays a major role in their emotional functioning prior to HCT.
66-A Poster: Importance of the physical therapist when assessing physical risk of patients targeted for home-based Cardiac Rehabilitation

Presenter: Rebecca Smith, Post-Doctoral Fellow

Geriatric Medicine

Research Interest: Clinical

Mentors: Daniel Forman MD

Funding Source: None

Authors: Rebecca Smith MPT, Kelly Allsup BS, Andrew Althouse PhD, Nicholas Bello BS, Karen Tarolli CRNP, Thomas Byard MS, Derek Coughenour MPH, Gavin Hickey MD, Nicole Lemieux MD, Daniel Forman MD

Introduction: To refine methods of physical risk assessment for patients enrolling in home-based phase II cardiac rehabilitation (CR). Participation in CR has AHA/ACC class I support for secondary prevention and risk reduction for coronary heart disease, and has been found to decrease mortality after a cardiac event. The alternate of home-based CR has been promulgated as a way to increase CR’s accessibility and application. However, it is necessary to develop a standardized approach to clarify which CR patients are safe to exercise at home. The physical therapist (PT) provides particular expertise at delineating pertinent risks of falls, poor endurance, and frailty, as part of the initial evaluation. Eligibility for home-based CR is contingent on the PT’s evaluation.

Methods: At the VA Pittsburgh Healthcare System, the PT plays an important role in each CR patient’s initial evaluation. Falls, endurance, and frailty are assessed as an aggregate evaluation. The PT works with physicians to determine which CR program would best meet the patient’s needs. Based on assessments of physical and medical risks, patients are stratified as low, moderate, or high risk to participate in CR. Those who are low risk are eligible for home-based CR. This entails use of equipment in patient’s home, a walking regimen or use of a local gym. Patients are also given a workbook with pictures for strengthening, balance, and stretching exercises. For high risk patients, the PT creates a more personalized exercise plan including aerobic conditioning, strengthening, gait, and balance training. This enables patients to get the therapeutic aerobic conditioning and strengthening they need despite their complex medical and physical limitations.

Results: 228 patients have been enrolled in CR since July 2015. Of those, 138 have been found to be low risk, 60 moderate risk and 25 high risk. 57 of the low risk patients have chosen to enroll in the home-based CR. Patients enrolled in home-based CR have been able to exercise safely and effectively with aerobic and strength improvements. Similarly, gains in 6 minute walk distance and the Duke Activity Scale score have been demonstrated.

Conclusion: The PT is an integral member of the CR team. PT’s knowledge of falls, endurance, and frailty, as well as their insights regarding exercise safety are critical assets for a patient-centered program. Patients who undergo a thorough physical assessment at the time of CR enrollment are able to have a program tailored to their (specific) needs, including the option of home-based care that is reliably safe and effective.
**Introduction:** The incremental prognostic influence of adverse right ventricular (RV) remodeling on LV stroke work in patients with pulmonary hypertension (PH) is still unclear. The objective of this study was to test the hypothesis that RV remodeling and LV stroke work index (LVSWI) by three-dimensional (3D) wall motion tracking analysis have additive prognostic value for clinical outcomes in patients with PH.

**Methods:** We studied 103 patients with pre-capillary PH (age, 58.2±13.2 years; 65% women). All patients had both 3D echocardiography (Artida, Toshiba Corp.) using wall motion tracking and right heart catheter studies. We obtained LV volume, RV volume from 3D full-volume echo data set. LV stroke work index was calculated by the combination of hemodynamic and 3D echocardiographic parameters: LVSWI = 0.0136 (mean blood pressure of peripheral artery - pulmonary artery wedge pressure) x (LV end-diastolic volume - LV end-systolic volume) / body surface area. Routine clinical and echo data were also obtained: NYHA functional class, tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC) and tricuspid regurgitation (TR) velocity. Clinical outcome events over 1 year were predefined as death, lung transplantation, and heart failure hospitalization.

**Results:** Of 103 patients, RV end-systolic volume index (RVESVI) was 72.3 ± 32.0 ml/m2, and LVSWI was 27.8 ± 13.0 cJ. RVESVI was positively correlated with invasive pulmonary vascular resistance (PVR) (r = 0.454, p < 0.001). LVSWI was inversely correlated with PVR (r = -0.430, p < 0.001) and RVESVI (r = -0.428, p < 0.001). There were 47 PH patients (46%) with unfavorable clinical outcome events over 1 year. We defined large RVESVI as =62.5 ml/m2 (median value), and low LVSWI using =26.9 cJ (median value). Kaplan-Mayer analysis showed that the subgroup of patients with both large RVESVI and low LVSWI had the worst outcomes (Log-rank, p < 0.001). In sequential Cox model, baseline clinical variables (?2 = 30.3) were improved by the addition of conventional echocardiographic parameters (?2 = 44.0, p < 0.001), RVESVI (?2 = 53.9, p = 0.019), and further improved by the addition of LVSWI (?2 = 58.3, p = 0.035).

**Conclusion:** 3D functional assessment of RV remodeling and LV stroke work index have incremental prognostic influence in patients with pulmonary hypertension.
68-A Poster: Changes in sexual function among midlife women: “I’m older... and I’m wiser.”

Presenter: Holly Thomas, Junior Faculty
General Internal Medicine

Research Interest: Clinical

Mentors: Rebecca C. Thurston PhD, Sonya Borrero MD, Rachel Hess MD

Funding Source: PCOR K12 (AHRQ)

Authors: Holly N. Thomas MD, Megan Hamm PhD, Rachel Hess MD, Sonya Borrero MD, Rebecca C. Thurston PhD

Introduction: Quantitative studies indicate that women’s sexual function declines during midlife. However, qualitative approaches that allow women to speak their own words regarding their experiences may capture nuances and individual variations that quantitative studies miss. We gathered qualitative data among sexually active women aged 45-60 to explore women’s perceptions of changes in their sexual function over time and how women respond to these changes.

Methods: Twenty interviews and three focus groups were conducted by a trained facilitator using an interview guide (N=39); sessions were audio-recorded and transcribed. Codebook development by two investigators proceeded using an iterative process until a final codebook was agreed upon; the primary investigator then coded all data. A second investigator coded a randomly selected 10% of data and kappa scores were calculated for inter-coder reliability. Codes relating to changes in sexual function with aging were examined to identify key themes.

Results: The mean age was 58 (range 46-59); 53% were White, 36% were Black, and 10% were of another race. All but 2 women identified as heterosexual. Women experienced both negative and positive changes in sexual function with aging. The most common negative changes were decreased frequency of sex, lower libido, vaginal dryness, and difficulty reaching orgasm. More women attributed these negative changes to psychosocial stressors than biological factors such as menopause. For some women, partner issues, including partner health problems, relationship discord, and partner sexual dysfunction were a major source of negative sexual changes. Many women responded to negative changes with adaptations, including changes in sexual behavior (e.g., using lubricants) and changing the aspects of sex they valued most highly (e.g., valuing emotional intimacy over achieving orgasm). There were a number of women who experienced positive changes in sex with aging; many felt that while frequency of sex had decreased, their satisfaction with sex had increased. They attributed these positive changes to higher self-confidence, increased self-knowledge, and better communication skills as they aged.

Conclusion: Negative changes in sexual function are common as women move through midlife. However, positive changes were also observed. Many women adapt to negative changes by modifying their sexual behavior or changing what aspects of sex they value most highly. Providers should recognize that not all changes are attributable to biological factors; psychosocial and interpersonal factors also play a role. Women have a wide range of responses to changes in sexual function with aging, highlighting the importance of assessing not only physical sexual function, but also overall sexual satisfaction.
**69-A Poster:** Poor Sleep is Associated with Recurrent Falls among Older Women in the Study of Osteoporotic Fractures

**Presenter:** Shachi Tyagi, Junior Faculty Geriatric Medicine

**Research Interest:** Clinical Geriatric Medicine

**Mentors:** Neil Resnick MD, Susan Greenspan MD, Daniel Buysse MD

**Funding Source:** P30 AG024827 (Greenspan)

**Authors:** Shachi Tyagi MD, Subashan Perera PhD, Joseph Hanlon PhD, Daniel Buysse MD

**Introduction:** Among the elderly, sleep disturbances and use of sedative medications for the treatment of sleep disturbances are both considered a strong risk factor for falls, but little is known about the association of recurrent falls with specific sleep disturbances namely poor sleep quality and daytime sleepiness individually or in aggregate or the impact of sedative use. We examined the association of subjective sleep disturbances—poor sleep quality and excessive daytime sleepiness among sedative users and non-users, with recurrent falls.

**Methods:** This cross sectional analysis from the Study of Osteoporotic Fractures used following variables collected at visit 8: excessive daytime sleepiness (defined as Epworth sleepiness scale score of >10), poor sleep quality by self-report (Pittsburgh Sleep Quality Index score of >5), and self-report of recurrent falls as >1 in the following year. Analyses were stratified by use of sedative medications (including antihistamines, sedative antidepressants, sedative benzodiazepines, benzodiazepine receptor agonists, and supplements—melatonin, valerian) because these medications affect both sleep and falls. Covariates were age, BMI, self-rated health, depression, anxiety, use of assistive device, poor vision, and comorbidities. Analyses used was logistic regression, the outcome being recurrent falls (faller yes/no); each sleep measure, sedative use and their interaction as main factors of interest. We included all covariates as additional independent variables to obtain adjusted odds ratios.

**Results:** There were 3549 participants (mean age 84 ± 3 years, 19% recurrent falls). Individual sleep disturbances of excessive daytime sleepiness and poor sleep quality were significantly associated with recurrent falls but among the sedative non-users only- (Adjusted Odds Ratio=OR=1.53 [1.20-2.12], p=.01) and (OR=1.28 [1.02-1.60], p=.03 respectively). Participants without sedative use but reporting both excessive daytime sleepiness and poor sleep quality had 99% increased risk of recurrent falls in the following year (OR=1.99 [1.38-3.04], p=.001) while the risk among those with persistent sleep disturbance despite the use sedatives was not significant (OR=1.80 [0.57-5.68], p=.32).

**Conclusion:** Excessive daytime sleepiness and poor sleep quality are associated with recurrent falls in women independent of sedative medication use.
70-A Poster: Ideal Cardiovascular Health Metrics in Couples: A Community-based Population Study

Presenter: Oluremi Ajala, Post-Doctoral Fellow Research Interest: Health Services/General Internal Medicine

Mentors: Steven Reis MD, Samir Saba MD Funding Source: University funds

Authors: Oluremi Ajala MD, Sebhat Erqou MD, Claudia Bambs MD, Andrew Althouse PhD, Michael Sharbaugh MPH, Samir Saba MD, Steven Reis MD

Introduction: Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality. Better understanding of CVD determinants is needed to decrease CVD risk. We hypothesized that ideal CVD health metrics are mostly concordant among heterosexual spousal or cohabitating couples.

Methods: We evaluated ideal CVD health metrics in the community-based Heart Strategies Concentrating on Risk Evaluation (HeartSCORE) study, which includes 231 couples. Ideal CVD health metrics as defined by the American Heart Association (AHA) comprises: non-smoking, body mass index <25kg/m2, physical activity at goal, diet consistent with guidelines, untreated total cholesterol <200mg/dL, untreated blood pressure <120/80mmHg, and untreated fasting glucose <100mg/dL. We used Fisher’s exact test and logistic regression to assess concordance patterns in these variables among couples.

Results: There was a low prevalence of ideal CVD health variables among the 462 participants (mean age 61 years, 22% Black). CVD health metrics with highest concordance (both partners achieving ideal target) were non-smoking (26.1%), ideal fruit and vegetable consumption (23.9%) and ideal fasting blood glucose (35.6%). The strongest intra-couple concordance was for smoking (odds ratio [OR]: 3.6, p<0.001), fruit and vegetable consumption (OR: 4.8, p<0.001) and blood pressure (OR: 3.04, p= 0.034). For discordant variables in couples, females were more likely to meet ideal CVD health metrics than males. None of the couples met ≥5 components of the ideal CVD health metrics. Only 9 (3.9%) couples had both members meeting ≥4 components of the ideal CVD health metrics, while 35 (15.2%) met ≥3 components. An individual had 3-fold higher odds of attaining 3+ ideal CVD health factors if they have a partner who attained 3+ components (OR 3.0, 95% CI=1.6-5.6). The corresponding OR for meeting 4+ ideal health factors was 5.1 (95% CI 1.9-13.7).

Conclusion: Our data suggest that incorporating couple-based interventions in addressing CVD health risk factors may be useful for improving specific factors. Fruit and vegetable consumption and smoking may be particularly good targets for such interventions.
**71-A Poster:** Hospital Perceptions of Medicare's Sepsis Quality Reporting Initiative

**Presenter:** Ian Barbash, Post-Doctoral Fellow  
**Research Interest:** Health Services/  
**Mentors:** Jeremy Kahn MD  
**Funding Source:** Individual NRSA (F32)

**Authors:** Ian Barbash MD, Kimberley Rak PhD, Courtney Kuza MPH, Jeremy Kahn MD

**Introduction:** In October 2015 the United States Centers for Medicare & Medicaid Services began requiring that US hospitals report on their compliance with a multi-component treatment bundle for patients with sepsis—a program known as “SEP-1”. Understanding how hospitals perceived and responded to SEP-1 is a critical first step in evaluating the program’s impact on sepsis treatment and outcomes.

**Methods:** We conducted semi-structured telephone interviews with hospital quality officers from a stratified random sample of non-federal hospitals in the United States, sampling hospitals based on size, teaching status and ownership. The interview script addressed four domains: structure and nature of the hospitals’ sepsis quality improvement initiatives before and after the Medicare reporting program; reception of the hospital responses by clinical staff; the approach to data abstraction and reporting; and overall impressions of the program’s impact. The interviews were recorded, transcribed, and coded for content and emergent themes by three independent coders. Discrepancies among coders were resolved through iterative group discussion. Interviews and analysis proceed concurrently until thematic saturation was achieved.

**Results:** We completed 29 interviews before achieving thematic saturation. Hospitals reported a variety of actions in response to SEP-1, including efforts to collect data, improve sepsis diagnosis and treatment, and manage clinicians’ attitudes toward SEP-1. These efforts required dedicated resources to meet the program’s requirements for treatment and documentation, which were thought to be overly broad and not consistently linked to patient-centered outcomes. Although most respondents felt that SEP-1 was likely to improve sepsis outcomes, they also described specific revisions that could improve its effectiveness, including providing hospitals with additional flexibility to focus on treatment processes most directly associated with improved patient outcomes, aligning the measures sepsis definitions with current clinical definitions, and restricting the measure to elements that can be collected electronically rather than manually.

**Conclusion:** Hospitals are responding to Medicare’s sepsis quality reporting mandate with varying intensity, but in ways that consistently require dedicated resources. Optimizing the effectiveness of the SEP-1 program may require revisions that provide hospitals the flexibility to focus on treatment processes with the most direct impact on patient-centered outcomes, as well as electronic approaches that improve sepsis identification and treatment while reducing the burden of quality measurement and reporting.
**Introduction:** There is systematic undercoding of medical comorbidities within administrative claims in the Veterans Health Administration (VA) as compared to Medicare. This undercoding may lead to bias when applying claims-based risk adjustment indices to compare medical outcomes between VA and Medicare. Medication-based risk adjustment models may be an unbiased method of risk adjustment in these circumstances. Our objective was to adapt a medication-based risk index for use with combined VA and Medicare data and compare its prognostic accuracy to commonly used claims-based risk adjustment methods in predicting 1-year mortality.

**Methods:** Our cohort included a convenience sample of all individuals enrolled in both VA and Medicare Part D who filled at least one opioid prescription from either system in 2012. We adapted an existing VA-based medication risk index (Rx Risk-V) to also incorporate Medicare pharmacy and durable medical equipment claims. Using the C-statistic (C), we compared the prognostic accuracy of the adapted Rx Risk-V + demographics (age, gender, race, Medicaid eligibility, and disability status) in predicting 1-year mortality to models that included demographics with and without alternative risk adjustment methods (prescription count, Charlson index, or Elixhauser index). We also compared the adapted Rx Risk-V model to models that included demographics, adapted Rx Risk-V, and Elixhauser or Charlson. We conducted a sensitivity analysis by restricting our cohort to dual enrollees who had a clinical encounter and/or received a medication within both VA and Medicare (i.e. dual users).

**Results:** The 271,343 Veterans in the overall cohort had a mean age of 70.5 years; 96.1% were male, 81.7% were non-Hispanic white, and 63.4% were dual users. Overall, 9.4% died within 1 year. The prognostic accuracy of the adapted Rx Risk-V (C=0.76) was significantly greater than models using demographics alone (C=0.72) or a prescription count (C=0.74), but significantly lower than models using Charlson (C=0.79) or Elixhauser (C=0.79) (P<0.001 for all comparisons). The model combining demographics, adapted Rx Risk-V, and Charlson provided significantly greater prognostic accuracy than all other models (C=0.80, P<0.001). We found similar patterns of relative model performance in analyses limited to dual users.

**Conclusion:** The adapted Rx Risk-V index, when used in combination with common claims-based indices, enhances prognostic accuracy in regard to 1-year mortality. Using this model in place of claims-based indices marginally lowers prognostic accuracy, but remains a viable method of risk adjustment when medical claims are not available or the use of claims-based indices may lead to bias.
Poster Abstracts

74-A Poster: VA Physicians’ Perspectives and Experiences Regarding Prescription Drug Monitoring Programs: A Multi-State Qualitative Study

Presenter: Thomas Radomski, Junior Faculty General Internal Medicine

Research Interest: Health Services/ Clinical Epidemiology

Mentors: Walid Gellad MD, MPH, Michael Fine MD, Joshua Thorpe PhD

Funding Source: VA Merit Award (Gellad), KL-2 (Radomski)

Authors: Thomas Radomski MD, Felicia Bixler MS, Susan Zickmund PhD, Katielynn Roman BS, Jennifer Hale BS, Leslie Hausmann PhD, Carolyn Thorpe PhD, Joshua Thorpe PhD, Katie Suda PharmD, Kevin Stroupe PharmD, Francesca Cunningham PharmD, Adam Gordon MD, Chester Good MD

Introduction: Although the Veterans Health Administration (VA) has implemented robust strategies to monitor prescription opioid dispensing, these strategies do not account for opioids prescribed to thousands of VA patients by providers outside the VA. State-based Prescription Drug Monitoring Programs (PDMPs) track dispensed opioid prescriptions and are a potential tool to identify VA patients’ receipt of opioids from non-VA sources. Our objective was to evaluate VA physicians’ perspectives and experiences regarding use of PDMPs to monitor Veterans’ opioid use from non-VA sources.

Methods: From 2/2016 – 8/2016, we interviewed 42 VA primary care physicians who had prescribed opioids to =15 Veterans in 2015. We sampled physicians from 2 states with PDMPs (MA, IL) and one state without physician access to a PDMP (PA). We conducted semi-structured telephone interviews that addressed the following topics regarding PDMPs: overall perceptions and experiences, ideas to improve use, and barriers/facilitators to use. Interviews were audio-recorded and transcribed verbatim. Two qualitative analysts developed a codebook, independently coded 20% of the transcripts, and assessed inter-coder reliability (kappa=0.70) before the master coder coded the remaining transcripts.

Results: We identified 3 overarching themes. First, physicians universally supported PDMPs (MA, IL) or desired access to one (PA), despite noting additional time and administrative burdens associated with their use. To improve use, physicians suggested: 1) linking PDMPs with the VA electronic health record, 2) using templated notes to document PDMP use, and 3) delegating PDMP queries to ancillary staff. Second, PDMP use challenged physicians’ underlying biases regarding opioid misuse. “I used to make a value judgement of my patients and made prescribing choices based upon that,” said one physician. “And in doing this (using a PDMP), I’ve realized that all of those things have to go out the window.” Third, physicians felt the limited data contained within their state’s PDMP was a barrier to optimal use. One physician said, “It (the PDMP) only gives me information about Massachusetts. So, for our patients who might be accessing medications in bordering states – I have no idea if that’s happening or not, and I wish I did.”

Conclusion: VA Physicians uniformly embraced and presented solutions to improve PDMPs as a tool to monitor Veterans’ opioid use from non-VA sources. Our findings can help the VA meet the requirements of the Comprehensive Addiction and Recovery Act, which requires use of PDMP data by VA physicians, and may also inform efforts outside the VA to implement use of PDMPs into practice.
75-A Poster: Does formal training in medical education and professional development lead to better career outcomes for clinician educators? A survey study of a degree granting program in medical education.

Presenter: Amar Kohli, Junior Faculty
General Internal Medicine

Research Interest: Medical Education

Mentors: None

Funding Source: GIM Award

Introduction: While faculty development programs are common, as of 2012, formal degree-granting programs in medical education existed at only ten institutions in the United States. To date, there have been limited outcomes reported for participants of degree-granting programs. Beginning in 2002, the University of Pittsburgh's Institute of Clinical Research Education created both masters and certificate level degree-granting programs in medical education, which now have more than 10 years of graduates. We sought to evaluate the program by surveying its participants with regards to their attitudes, self-reported skills, and career outcomes.

Methods: All graduates of the program between 2004 and 2014 received an email invitation to complete an anonymous electronic survey regarding their satisfaction with the program as well as their perception of whether the master's program adequately prepared them in domains pertinent to medical educators. Participants were also asked to upload their current CV from which data about educational leadership positions, curriculum development and national dissemination of education-related work was abstracted.

Results: Out of 60 graduates, 47 completed the survey (78%) and out of those 45 uploaded their CV for analysis (75%). More than 90% of respondents agreed that due to completion of the program they were competent in applying principles of learning theory, clinical teaching, small group teaching, ability to give lectures, providing feedback to learners, curriculum development and evaluation, as well as conducting and evaluating educational research. 94% of respondents believed that they were a more effective educator than peers who did not complete a degree. CV abstraction revealed that 98% of respondents hold academic positions. Respondents represent more than 15 different medical specialties, though the majority (40%) are general internists. Of graduates surveyed, 76% held educational leadership positions. 93% published in peer reviewed journals, 67% published on an educationally related topic, 87% participated in curriculum development, and 67% engaged in mentorship. 13 respondents won teaching awards at their respective institutions.

Conclusion: Because degree-granting programs in medical education require great resource investment, the outcomes of such programs are relevant for institutional support and sustainability. Graduates of the degree granting programs at the University of Pittsburgh reported, because of their training, competence in several key domains crucial to success as a clinician educator. Abstraction of CV's noted almost all hold academic positions in their representative specialties as well as document their prolific nature in several domains essential to academic success as a clinician-educator.
**Introduction:** Quality improvement (QI) plays a crucial role in practice management, assessment, and reimbursement, and is included in the ACGME requirements. How QI is taught to internal medicine residents is variable due to clinic resources, competing didactics, limited time, knowledge, and motivation. Literature on the effect of QI curricula on resident patient outcomes is limited. We previously presented our QI curriculum at one site for one academic year (AY). We assessed its effectiveness on resident patient outcomes at 3 sites over 2 AYs.

**Methods:** A longitudinal curriculum was designed to simulate the Plan-Do-Study-Act cycle of QI. Each site’s residents developed and implemented new QI projects each AY based on their site residents’ quality metrics and institutional needs. This was implemented at 3 sites with varying resources: a large academic center, community-based clinic, and VA-based clinic. AY1 was 9/2014-6/2015, and AY2 was 9/2015-6/2016. Major themes included: 1) brief didactics on QI principles and identification of QI projects; 2) creation of aim statements using resident panels’ quality metrics; 3) collaboration between residents and staff to form a “QI council” that determined practice/provider/patient interventions to achieve aims; 4) provision of timely data for continuous re-evaluation. The academic center’s QI projects were diabetic foot and eye exams in AY1 and blood pressure (BP) control in AY2; the community-based site chose diabetic foot exams for AY1 and eye exams for AY2; and the VA site chose BP control in AY1 and diabetic BP control for AY2. We show effectiveness through quality metric rates from quarterly quality reports.

**Results:** There were 137 residents (56 residents each at the academic and VA sites and 25 residents at the community clinic). At the academic center, resident foot exams increased from 64% to 78% and eye exams increased from 42% to 69% in AY1. BP control increased from 51% to 61% in AY2. At the community clinic, resident foot exams increased from 59% to 66% in AY1 and eye exams increased from 44% to 77% in AY2. At the VA, BP control increased from 67% to 87% in AY1 and diabetic BP control increased from 75% to 90% in AY2.

**Conclusion:** Our curriculum was successfully implemented at 3 sites with varying resources and QI projects. We showed dramatic improvements in resident patient outcomes for each QI project at the end of their respective AY. Future research will need to assess sustainability of previous QI projects as new projects are selected.
77-A Poster: Plasma Sodium Correction Practices in Patients admitted with Hyponatremia at UPMC Presbyterian and Montefiore Hospitals during 2015

Presenter: Helbert Rondon-Berrios, Junior Faculty Renal-Electrolyte Research Interest: Medical Education

Mentors: None Funding Source: None

Authors: Julio Pena-Polanco MD, Rohan Paul MD, Eric Ong MD, Roy Shamir MD, Helbert Rondon-Berrios MD

Introduction: Hyponatremia is the most common electrolyte disorder and is associated with increased morbidity and mortality. However, complications can arise from its correction including osmotic demyelination syndrome (ODS). To prevent this, it is imperative that plasma sodium (PNa) correction meets specific goals and limits. Recent guidelines have issued recommendations regarding goals and limits of correction. Nevertheless, studies show that nonoptimal correction of hyponatremia is still common. The objective of this study is to determine the proportion of nonoptimal correction of PNa by 24h of admission in patients admitted to UPMC Presbyterian and Montefiore hospitals with hyponatremia during 2015.

Methods: After obtaining approval from QI committee, a retrospective chart review was performed. Patients with PNa<125 mEq/L admitted to UPMC Presbyterian and Montefiore hospitals in calendar year 2015 were included. Patients with incomplete data, on dialysis, or who developed hyponatremia during hospitalization were excluded. For recurrent admissions, only earliest admission was considered. PNa was corrected for plasma glucose=200 mg/dL if a simultaneous glucose measurement was available. First PNa on admission was labeled PNa0. PNa at precisely 24h of admission (PNa24) was universally absent therefore PNa24 was estimated using a validated formula. Degree of correction at 24h(?PNa) was calculated as PNa24–PNa0. Outcomes were adjudicated as overcorrection(?PNa>8 or 10 mEq/L depending on ODS risk), undercorrection(?PNa<4 mEq/L) and proper correction(the rest). Other covariables that might influence the outcomes were also considered. Strength of the association between covariables and outcomes was measured with chi-squared and Fischer's Exact tests.

Results: 228 patients were identified meeting inclusion criteria. Hyponatremia was corrected properly in 71 patients(31.2%). Hyponatremia was overcorrected in 60 patients (26.3%) and undercorrected in 97 patients(42.5%). No cases of ODS were observed. Overcorrection of hyponatremia was significantly associated with 3 or less PNa measurements by 24h(p=0.02). Overcorrection of hyponatremia was not significantly associated with hyponatremia etiology, overcorrection risk factors, therapeutic interventions, hospital setting, admitting service, or Nephrology consultation. Nephrology consultation occurred in 31.6% of all cases.

Conclusion: Nonoptimal correction of hyponatremia is common and is associated with infrequent PNa measurements. ODS remains rare despite common overcorrection. A hospital-wide educational intervention on hyponatremia emphasizing proper therapy of hyponatremia including goals and limits of correction as well as prevention and management of overcorrection is needed.
**78-A Poster:** Overexpression and Hypoglycosylation of MUC1 is Associated with Endoscopic Recurrence of Post-operative Crohn's disease

**Presenter:** Jana Al Hashash, Junior Faculty  
**Research Interest:** Translational Gastroenterology, Hepatology and Nutrition

**Mentors:** Olivera (Olja) Finn PhD, Miguel Regueiro MD, David Binion MD  
**Funding Source:** None

**Authors:** Jana Al Hashash MD, Pamela Beatty PhD, Kristen Critelli MD, Matthew Regueiro, Douglas Hartman MD, Miguel Regueiro MD, David Binion MD, Kimberly Goldby-Reffner RN, BS, CCRC, Olivera Finn PhD

**Introduction:** MUC1 is an epithelial cell mucin that contributes to mucosal homeostasis and plays a protective role against inflammation. In the setting of inflammation and cancer, MUC1 is overexpressed and hypoglycosylated (i.e., abnormal MUC1 form). Studies showed that overexpression and hypoglycosylation of MUC1 drive chronic inflammation and progression to colitis associated colon cancer in IBD mouse models. Intervention with a vaccine against abnormal hypoglycosylated MUC1 administered early in life ameliorated subsequent progression to IBD and cancer in mice that spontaneously develop IBD. Association of hypoglycosylated MUC1 expression with clinical course of human IBD is not defined. We sought to evaluate if overexpressed and hypoglycosylated MUC1 is associated with emergence of inflammation in the neo-terminal ileum biopsies of patients with post-operative Crohn's disease (CD). We hypothesized that overexpression and hypoglycosylation of MUC1 is associated with more severe endoscopic post-operative CD recurrence (i2,i3,i4).

**Methods:** Archived neo-terminal ileum biopsies from patients who had undergone curative ileocecal resection for CD were included. All patients had Rutgeerts’ endoscopic ileal recurrence score recorded at time of colonoscopy (i0 to i4). Consecutive tissue sections were stained using 2 different anti-MUC1 antibodies; (1) HMPV recognizes all MUC1 (normal glycosylated and abnormal hypoglycosylated), while (2) 4H5 recognizes only abnormal (hypoglycosylated) MUC1.

**Results:** A total of 62 post-operative CD patients were evaluated. 18 had an endoscopic score of i0, with 3 patients (17%) showing high levels of MUC1 but none were the abnormal hypoglycosylated form. Of the 11 patients with i1 score, 4 (36%) expressed high levels of MUC1, but none were the abnormal hypoglycosylated MUC1 form. Of the 16 patients with i2 score, 4 patients (25%) had elevated MUC1 with 1 patient demonstrating high levels of hypoglycosylated form. All 7 i3 patients (100%) had elevated MUC1 with 57% (4 patients) expressing elevated hypoglycosylated form. Amongst post-operative patients with the most severe epithelial damage (Rutgeerts i4), 60% of the 10 patients had elevated MUC1 levels and 2 of these patients had high expression of abnormal hypoglycosylated MUC1.

**Conclusion:** High MUC1 expression is associated with severe post-operative endoscopic recurrence in the majority of CD patients with i3 and i4 scores. High levels of hypoglycosylated MUC1 was only seen in the setting of significant endoscopic recurrence (Rutgeerts i2, i3, i4). Given the ongoing application of human hypoglycosylated MUC1 vaccine trials to prevent polyps/colon cancer, further studies characterizing the biology of high hypoglycosylated MUC1 expression in CD inflammation are warranted to lay foundation for a vaccine trial to prevent recurrence of post-operative CD.
Poster Abstracts

79-A Poster: Functional brain connectivity during urgency urinary incontinence

Presenter: Becky Clarkson, Junior Faculty
Geriatric Medicine

Research Interest: Translational

Mentors: None

Funding Source: Post hoc analysis of R01 funded study

Authors: Becky Clarkson PhD, Helmet Karim MS, Derek Griffiths PhD, Neil Resnick MD

Introduction: Urgency urinary incontinence (UUI) is prevalent, morbid and costly, especially among older adults. Investigation of UUI has traditionally ignored the brain and instead focused on bladder function. This post hoc analysis is based on functional brain imaging data obtained during urgency provocation in women with UUI, both before and after therapy. The dataset allowed comparison of incontinent and continent women, highlighting active mechanisms that may be related to continence status and response to therapy. Here we present the functional connectivity between each brain region of interest (RoI) involved with bladder control.

Methods: Urge urinary incontinence (UUI) is prevalent, morbid and costly, especially among older adults. Investigation of UUI has traditionally ignored the brain and instead focused on bladder function. This post hoc analysis is based on functional brain imaging data obtained during urgency provocation in women with UUI, both before and after therapy. The dataset allowed comparison of incontinent and continent women, highlighting active mechanisms that may be related to continence status and response to therapy. Here we present the functional connectivity between each brain region of interest (RoI) involved with bladder control.

Results: During urgency, connectivity between regions of interest did not differ significantly pre-treatment between the three groups although we did find some trends. Specifically, non-responders had higher dACC-insula connectivity than both responders and controls (p=0.037), and, as compared with both non-responders and controls, responders had higher mPFC to mid-cingulate connectivity (p=0.037) and greater mPFC-dACC connectivity (p=0.005). Baseline voxel-wise analyses showed that insula – primary visual cortex connectivity was high in responders but no different in non-responders (continent showed lower connectivity during urgency). The mPFC – midcingulate connectivity at baseline was greatest in responders compared to controls, and both were higher than seen in non-responders. Responders showed a decrease in dACC – primary visual cortex and insula – primary motor/sensory cortex connectivity, which was not present in non-responders.

Conclusion: This analysis extends our prior findings and identifies how connectivity between pairs of key regions involved in bladder control differs between controls, responders and non-responders, and also how connectivity changes with therapy.
**80-A Poster:** Phase IB Study of Pembrolizumab (Pembro) and Pegylated-interferon alfa-2b (Peg-IFN) in Advanced Melanoma (MEL).

**Presenter:** Diwakar Davar, Junior Faculty Research Interest: Translational Hematology/Oncology

**Mentors:** Hassane Zarour MD, John Kirkwood MD Funding Source: Melanoma Research Alliance, ASCO/CCF

**Authors:** Diwakar Davar MD, Hong Wang PhD, Pooja Pawar MS, Joe-Marc Chauvin PhD, Zhaojun Sun PhD, Ornella Pagliano PhD, Julien Fourcade PhD, Amy Rose BS, Cindy Sander MS, Ahmad Tarhini PhD, John Kirkwood MD, Hassane Zarour MD

**Introduction:** Overall responses (OR) are reported in 34% of patients (pts) with advanced MEL treated with Pembro. Landmark survival is 66%/49% at 1-/2-years respectively. Pre-existing CD8+ T-cell infiltrates and IFN gene signature at tumor sites correlate with response to PD-1 blockade. To evaluate synergy between PD-1 blockade and Peg-IFN, we implemented a phase Ib study of Pembro/Peg-IFN combination with dose-seeking and dose-expansion phases in stage IV MEL.

**Methods:** 43 pts with IV MEL were enrolled. Peg-IFN was dose-escalated using modified toxicity probability interval (mTPI) design in 3 cohorts (4 pts each) at 1,2 and 3 mcg/kg SC while Pembrolizumab was dosed at 2mg/kg q3weeks in all pts. Primary endpoints were safety and incidence of dose-limiting toxicities (DLTs). Secondary endpoints were OR rate (ORR), progression free and overall survival. Response was assessed every 12 weeks (RECIST 1.1). Sequential blood draws and tumor biopsies were collected.

**Results:** 43 pts with advanced MEL were enrolled (33 cutaneous, 3 mucosal, 7 with no primary) to 3 dose-levels. Disease sub-stage is as follows: 13/43 (30.2%) M1a, 12/43 (27.9%) M1b, 18/43 (41.9%) M1c. 9/43 pts (20.9%) had treated CNS metastases while 6/43 (14.0%) had elevated LDH. 35.3% were BRAF mutant while 5.9% were NRAS mutant. 16/43 (37.2%) had prior Ipilimumab; 5/43 (11.6%) = 2 lines of systemic therapy. G1/2 toxicities included anemia, nausea, hyponatremia and transaminitis. G3 toxicities of note included rash (11%), hyponatremia (15%), neutropenia (15%) and fatigue (30%). No DLTs were observed. Pembro 2mg/kg + Peg-IFN 3mcg/kg identified as RP2D – to which 31 further pts were enrolled. Responses were seen at all 3 dose levels among 34 evaluable pts. Best overall response rate was 47.1% while current response rate is 35.3%. Autoimmune toxicities included adrenal insufficiency and Vogt-Koyonagi-Harada uveitis seen in 2 pts with ongoing PR off therapy.

**Conclusion:** Pembro/Peg-IFN combination has an acceptable toxicity profile and shows evidence of clinical efficacy in stage IV MEL. Median PFS/OS are 13.0/13.5 months and unreached in respondents. Whether Pembro/Peg-IFN combination is superior to Pembro alone in terms of clinical efficacy will need to be investigated in the context of a future randomized phase II trial. Ongoing correlative studies from peripheral blood and tumor samples obtained pre- and post-treatment include multiparameyer flow cytometry, RNAseq, TCR sequencing, multiplex immunohistochemistry and microbiome analyses to investigate potential biomarkers of clinical responses to the combinatorial therapy.
**81-A Poster:** Urinary Plasmin as a Predictor of Increased Blood Pressure and Decline in GFR in Diabetic Nephropathy

**Presenter:** John Demko, Medical Student  
Renal-Electrolyte

**Research Interest:** Translational

**Mentors:** Thomas Kleyman MD,  
Rebecca Hughey PhD

**Funding Source:** NIDDK T35 NRSA

**Authors:** John Demko BS, Evan Ray MD, PhD, Tina Costacou PhD, Rachel Miller PhD, Trevor Orchard MBBCh, Rebecca Hughey PhD, Thomas Kleyman MD

**Introduction:** In chronic kidney disease, proteinuria correlates with increased extracellular fluid volume (ECFV), increased blood pressure and decline in kidney function (eGFR). Mechanisms by which this occurs remain unclear. The serum fibrinolytic protease, plasmin, has been proposed to play a role. In proteinuric kidney disease, plasmin and its precursor, plasminogen, are aberrantly leaked through damaged glomeruli and can be detected in the urine. In vitro, plasmin can activate the epithelial Na channel (ENaC), suggesting that it may stimulate Na retention in the kidney, thereby contributing to increased ECFV and blood pressure. Urinary plasmin levels correlate with increased blood pressure. Additionally, plasmin is toxic to renal epithelial cells and may promote progression of kidney disease. We hypothesize that urinary plasmin levels predict subsequent increases in blood pressure or decline in eGFR.

**Methods:** Urine specimens and clinical data were prospectively collected from subjects with type I diabetes over 28 years through the Epidemiology of Diabetes Complications Study. Urinary plasmin/plasminogen concentration from 128 subjects was normalized to urinary creatinine (uPlg/Cr). uPlg/Cr was compared to blood pressure and number of anti-hypertensive medications at the time of urine collection. uPlg/Cr was then compared to subsequent changes in blood pressure, need for anti-hypertensive agents, and decline in eGFR. Regression analysis was applied to adjust for confounding variables, including urinary albumin, which increases as a function of blood pressure.

**Results:** In preliminary cross-sectional analysis, uPlg/Cr correlated with number of blood pressure medications, consistent with promotion of renal Na retention. Preliminary longitudinal analysis suggests that uPlg/Cr may correlate with decline in kidney function. Additional cross-sectional and longitudinal analyses are under way.

**Conclusion:** These findings address whether urinary plasmin may participate in promoting ECFV, hypertension, and progression of proteinuric kidney disease. Further, it examines whether it may be used as a predictive biomarker or therapeutic target to prevent increase in blood pressure and decline in kidney function in proteinuric kidney disease.
**Introduction:** Mast cells (MCs) and Type-2 inflammation are increased in asthma and often appear to be correlated (Dougherty, 2010). However, the relative contribution of each to asthma pathogenesis is unclear. In response to anti-human IgE-triggered activation, bronchoalveolar lavage (BAL) MCs degranulate and secrete eicosanoids (Flint, 1985; Pearce, 1987). MCs respond to Type-2 cytokines, but whether their response to anti-IgE differs in the presence of a Type-2 background is not clear. We hypothesized that Type-2 inflammation in asthmatics with evidence of airway luminal MCs would alter the MC functional response.

**Methods:** BAL cells from 45 asthmatics from University of Pittsburgh site of the Severe Asthma Research Program were suspended in media, incubated with and without anti-human IgE (Dako) for 20 minutes and releasates were assessed for PGD2 and tryptase by enzyme immunoassays. Subjects were classified as being MC “High” or “Low” based on the BAL cell tryptase mRNA median split. Peripheral blood eosinophilia (=300/microliter) and elevated airway epithelial eotaxin-3 mRNA (≥0.3, the median), were used to indicate Type-2-inflammation. Using both Type-2 biomarkers, subjects were grouped into quadrants (MC High/Low and Type-2 High/Low) and analyzed in relation to release of MC mediators following stimulation. For each subject, the fold changes for tryptase and PGD2 (stimulated/unstimulated) were calculated from total BAL cell population and normalized to baseline BAL cell tryptase mRNA to control for varying MC numbers.

**Results:** BAL cell tryptase mRNA was highest in the MC High/Type-2 High asthma quadrant using either Type-2 biomarker (p<0.0001 for both). Following anti-IgE stimulation, MCs from the MC High/Type-2-High group released less tryptase protein than the MC Low/Type-2 Low group (p<0.0001 for either Type-2 biomarker, Figure 1A). The MC Low/Type-2 High released less tryptase than the MC Low/Type-2 Low implying that Type-2 inflammation attenuates MC mediator release per MC. The MC High/Type-2 High also generated significantly less PGD2 vs. all other quadrants (p<0.0001 for either Type-2 biomarker, Figure 1B). The MC High/Type-2 High quadrant, having BAL MC with the least mediator release, also had the most asthma exacerbations in the previous year (p=0.03).

**Conclusion:** The presence of chronic Type-2 airway inflammation, regardless of the level of BAL MCs, was associated with MCs having a diminished functional IgE response, but with subjects having more asthma exacerbations. While the mechanism(s) for these effects remains to be determined, the combination of a noninvasive biomarker of the airway burden of MCs along with the blood eosinophil count might better reflect asthma control.
**83-A Poster:** Inflammatory macrophage expansion in pulmonary hypertension depends upon mobilization of blood-borne monocytes

**Presenter:** Jonathan Florentin, Post-Doctoral Fellow  
**Research Interest:** Translational Vascular Medicine Institute

**Mentors:** Partha Dutta PhD, Stephen Chan MD  
**Funding Source:** NIH

**Authors:** Jonathan Florentin PhD, Emilie Coppin PhD, Yingze Zhang PhD, Annie Watson MPH, John Sembrat, Mauricio Rojas MD, Marc Simon MD, Stephen Chan MD, Partha Dutta PhD

**Introduction:** Background: Genetic and environmental stressors in the pulmonary vessels leads to local lung inflammation and correlates with the occurrence of vascular remodeling and dysfunction, eventually leading to pulmonary hypertension (PH). Previous studies reported an accumulation of perivascular inflammatory cells, particularly macrophages in the lungs of PH patients. However, the expansion of lung macrophages in PH is poorly understood. Furthermore, the role of monocytes in macrophage generation and lung remodeling in PH has not yet been defined. This study aimed to decipher the origin of the macrophage population in the lung of PH patients.

**Methods:** Methods: We analyzed myeloid cell populations in blood and lungs of mice exposed to 3 weeks hypoxia using a 12-color flow cytometry panel.

**Results:** Results: We observed 3 and 1.4 fold increase of both blood monocyte count and frequency, respectively, in mice after 3 weeks of hypoxia. Similar monocytosis was also observed in the blood of PH patients. When we assessed different inflammatory monocyte subsets in PH patients, we found 18 fold increase in CD14+CD16+ (non-classical) and 7 fold increase in CD14+CD16int (intermediate) monocyte subsets in the blood of PH patients compared to healthy control. Additionally, RNA expression of chemokines responsible for monocyte recruitment to the lungs, including CCL2 and CX3CL1, were elevated in mice after chronic hypoxia. Correspondingly, we found increased levels of the chemokines in the lungs of PH patients. Importantly, parabiosis between CD45.1 and CD45.2 mice exposed to chronic hypoxia demonstrated that approximately 70% of interstitial macrophages originated from monocytes in the blood.

**Conclusion:** Conclusions and Impact: In both rodent and human PH, we found an expansion of inflammatory blood-borne monocytes accompanied by increased chemokine levels that leads to translocation into the diseased pulmonary arterioles where they differentiate into macrophages. This study will investigate for the first time, the origin of the expansion of interstitial macrophages in the diseased lungs in PH delineating their relevance for triggering a pro-inflammatory milieu in the diseased lung microenvironment. This work will have a therapeutic component through the use of CX3CR1 and CCR2 KO mouse models. These molecules can be used as targets to decrease lung inflammation in the lungs of PH patients.
**84-A Poster:** Skin-resident effector memory CD8+CD28- T cells exhibit a pro-fibrotic phenotype in patients with systemic sclerosis

**Presenter:** Patrizia Fuschiotti, Junior Faculty  
**Research Interest:** Translational Rheumatology and Clinical Immunology

**Mentors:** Robyn Domsic MD  
**Funding Source:** R03 AR065755

**Authors:** Gang Li PhD, Adriana Larregina MD, Robyn Domsic MD, Donna Stolz PhD, Thomas Medsger MD, Robert Lafyatis MD, Patrizia Fuschiotti PhD

**Introduction:** Loss of CD28 expression by CD8+ T cells occurs with age and during chronic inflammatory conditions. CD8+CD28- T cells are a heterogeneous cell subpopulation whose function ranges from immunosuppressive to effector. Here we analyzed the role of CD8+CD28- T cells in the pathogenesis of systemic sclerosis (SSc), a connective tissue disorder characterized by autoimmunity, vasculopathy and extensive cutaneous and visceral fibrosis.

**Methods:** We purified CD8+ T cells from the blood and lesional skin of patients with SSc. Flow cytometry was used to determine cell surface expression of skin-homing receptors, markers of residency in the skin and phenotype. Cytokine production was determined by intracellular cytokine staining. Co-culture experiments were performed to determine the ability of SSc CD8+ T cells to induce a pro-fibrotic phenotype and tissue damage in dermal fibroblasts.

**Results:** The frequency of CD8+CD28- T cells is increased in the blood and affected skin of SSc patients, independent of patient age, and correlates with the extent of skin fibrosis. The majority of skin-tropic CD8+CD28- T cells are resident in the skin lesions of patients in the early stage of the disease, exhibit an effector memory phenotype and present a strong cytolytic activity ex vivo. Skin-resident and circulating SSc CD8+CD28- T cells produce high levels of the pro-fibrotic cytokine IL-13, which induces collagen production by normal and SSc dermal fibroblasts.

**Conclusion:** Our findings indicate that CD8+CD28- T cells represent a pathogenic T-cell subset in SSc and likely play a critical role in the early stage of SSc skin disease.
86-A Poster: Persistence of CD57+KLRG1+ Cytomegalovirus (CMV)-specific Effector CD8 T cells through the Primary, Contraction, and Chronic phase of CMV Infection is associated with Control of Relapsing CMV infection.

Presenter: Aki Hoji, Post-Doctoral Fellow
Research Interest: Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: John McDyer MD
Funding Source: R01

Authors: Aki Hoji PhD

Introduction: Cytomegalovirus (CMV) is the single most critical infectious agent that has a significant impact on morbidity and mortality of lung transplant. In this study, we embarked on characterizing effector phenotypes and functions of CMV-specific CD8+ T cells in primary CMV infection. Among our cohort of high risk D+/R- LTRs, CD57 and KLRG1 was extensively expressed and KLRG1 was a sole phenotypic marker that was the best correlated with relapsing viremic control. Moreover, KLRG1 expression was positively correlated with T-bet expression and the high polyfunctionality. Furthermore, CD57+KLRG1+ CMV-specific CD8+ T cells persist and even become enriched during and post a contraction phase of CMV infection.

Methods: PBMCs from D+/R- LTRs were stained with a series of CMVpp65-specific MHC dextramers and the panel of antibodies, and analyzed. Also, cells were stimulated in vitro for 6hrs with CMVpp65 antigens, and stained for cytokines. Also the proliferative capacity of cells was measured by dilution of CFSEDA labeled cells which were stimulated with CMVpp65 antigens for 7-days, followed by the flow cytometric analysis. Moreover, chromatin immunoprecipitation assay was performed to show T-bet biding to KLRG1 promoter. Data are presented as mean ± SEM, and p-value of less than 0.05 was considered statistically significant.

Results: In our LTR cohort (n=23), we found that CD57 (40.4 ± 6.9%) is co-expressed with KLRG1 and CD27 on bulk and CMV-specific CD8+ T cells in primary CMV infection. Also, CD57+ and KLRG1+CMV-specific CD8+ T cells (57.0 ± 8.7% and ) from the post CMV acute and contraction phase of CMV infection proliferate in response to CMV antigens in vitro, and such cells are highly multfunctional. Moreover, we demonstrated that T-bet expression was significantly correlated (R2=0.725, p<0.0001) with KLRG1 expression, and further showed a direct interaction of T-bet with the KLRG1 promoter. In addition, we identified KLRG1 as a sole marker of protective CMV-specific CD8+ T cells as its expression during a primary infection was the best correlated (p<0.0034) among other T cells differentiation markers with viremic control in LTRs.

Conclusion: Collectively, our results suggest that CD57 and KLRG1 may not be the immune senescent marker of T cells and NK cells but rather they appear to be more closely tied with maturation of effector T and NK cells in the absence of cellular senescence as depicted by a majority of current models. Overall, our results suggest the perseverance of CD57+KLRG1+ CMV-specific effector CD8+ T cells throughout the course of CMV infection is imperative for immune control of primary and relapsing CMV infection.
**87-A Poster:** High pulmonary arterial pressures are associated with decreased microbial nitrate metabolism in the mouth.

**Presenter:** Carl Koch, Post-Doctoral Fellow  
**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD, MS, Mark Gladwin MD  
**Funding Source:** Individual NRSA (F32)

**Authors:** Carl Koch MD, Adam Fitch BS, Marc Simon MD, Shulin Qin MD, Courtney Sparacino-Watkins PhD, Sofiya Rehman MD, Mark Gladwin MD, Alison Morris MD, MS

**Introduction:** Impaired signaling and production of nitric oxide (NO) are hallmarks of pulmonary hypertension (PH) pathogenesis. Dietary nitrate and nitrite from green leafy vegetables serve as NO donors under conditions of hypoxia and stress. However, bioactivation of nitrate in mammals requires unique bacterial nitrate reductase enzymes (NRs) from specific commensal oral and gut bacteria. As changes in the oral and gut microbiome have been linked to systemic vascular injury, inflammation and disease, we investigated the potential role of oral bacterial nitrate metabolism to impact pulmonary arterial (PA) pressures and the development of PH.

**Methods:** Oral wash (OW) from study participants undergoing right heart catheterization at the University of Pittsburgh underwent bacterial 16S ribosomal RNA sequencing and quantification using the Illumina MiSeq system and real-time PCR, respectively. Sequencing data were processed with Qiime and PICRUSt. Oral nitrate reductase enzyme activity was measured in OW via ex vivo reaction with nitrate under anoxia and normalized to 16S content. Non-parametric p-values with FDR correction are presented. Variables were transformed for normality where appropriate.

**Results:** Of 65 participants who were studied, 43% (28) were female, and 91% (59) were white. Median age was 59 (iqr 12) and BMI was 27.6 (iqr 7.5). Mean PA pressure (mPAP) did not differ by age, sex, race or BMI (p>0.05). Using 16S-based inference, the predicted relative gene content of the bacterial respiratory NR, nar, was found to be negatively correlated with mPAP (), suggesting that reduced capacity of oral bacteria to metabolize nitrate may be associated with higher mPAP. Next, the relationship between predicted NR gene content and measured oral nitrate reduction was confirmed via ex vivo NR enzyme activity assay, which revealed a striking positive association between predicted nar content and measured NR activity (). Further, the log ratio of the strongest positive (Micrococcaceae, ) and negative (Porphyromonadaceae, ) taxonomic family predictors of measured NR activity was found to strongly correlate with predicted nar gene content () and to show a significant negative correlation with mPAP), suggesting that the relative abundance of high to low nitrate reducing bacteria in the mouth could influence PA pressures via nitrate reduction.

**Conclusion:** High mean PA pressures are associated with a reduction in both predicted and measured oral microbial NR activity and a decrease in the ratio of high to low nitrate reducing oral bacteria, together providing early mechanistic evidence of a potential physiological link between oral microbial metabolic function and PH.
**88-A Poster:** Associations between Peripheral Blood Monocyte Surface Markers and Pulmonary Dysfunction in HIV-Infected Individuals

**Presenter:** Mariam Lawani, Medical Student  
**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD, MS, Meghan Fitzpatrick MD  
**Funding Source:** NIH K24 HL123342, R01 HL120398 (AM)

**Authors:** Mariam Lawani BSc, Meghan Fitzpatrick MD, Shulin Qin PhD, Joshua Michel BA, Jeffery Martinson BA, Ruth Greenblatt MD, Lawrence Kingsley DrPH, Laurence Huang MD, Alan Landay PhD, Adde De Vallejo PhD, Alison Morris MD, MS

**Introduction:** HIV-infected persons in the current era of highly active anti-retroviral therapy (HAART) have increased prevalence and early onset of chronic obstructive pulmonary disease (COPD). Both HIV and COPD are independently characterized by chronic inflammation and immune activation, and monocytes are key innate immune cells implicated in both diseases. Given that circulating monocytes replenish alveolar macrophages, whose number and function are altered during inflammatory lung diseases, the immune phenotype of monocyte subsets in the course of HIV-associated lung dysfunction warrants further study. Differential distribution of circulating monocyte subsets and surface marker expression may predict lung dysfunction in HIV-infected persons.

**Methods:** HIV-infected and uninfected persons with viably cryopreserved peripheral blood mononuclear cells (PBMCs), as well as clinical and pulmonary function test (PFT) data were included in the study. Monocyte subsets: classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical (CD14+CD16++) were quantified and phenotyped by flow cytometry for expression levels of monocyte activation (CX3CR1, CD11b, HLA-DR) markers. Relationships between the frequencies of monocyte subsets, their respective phenotypes and PFTs were tested by Spearman correlation or Ranksum. Multivariable models were used to adjust for clinically relevant variables.

**Results:** 79 participants were enrolled of whom; 61(77%) were HIV infected; mean age of 52 years and 28% were female. HIV infected persons had more tobacco exposure than HIV-uninfected (median pack-years 16.87 vs. 0.15 p=0.009). 95% of HIV-infected persons used HAART and 74% were virologically-suppressed. PFTs were normal on average, and there were no differences in PFTs by HIV status in this cohort. The intermediate (IM) monocyte subset, and certain inflammatory phenotypes (CD11b+ IM and CD11b+ CX3CR1+ NC) were more frequent in HIV-infected persons. In the HIV-infected group only, positive correlations were found between the number of circulation monocytes and FEV1 percent-predicted [ß =1.34 p =0.003]. The frequency of NC-monocytes was correlated with pre-bronchodilator FEV1/FVC [ß =3.95 p =0.006]. Correlations were also found between CX3CR1 expression on NC-monocytes and FEV1/FVC: pre-bronchodilator FEV1/FVC [p<0.006], post-bronchodilator FEV1/FVC [ß =3.87 p =0.011]

**Conclusion:** Monocyte subset distribution and activation vary with certain measures of lung function in HIV-infected individuals. The positive associations suggest an adaptive expansion of monocyte subsets that may initially compensate for lung dysfunction in HIV-infected individuals. Functional studies are required to correlate monocyte surface marker expression with disease phenotype in HIV-associated lung diseases.
89-A Poster: Associations between T Cell Exhaustion and Immunosenescence in HIV-associated Pulmonary Dysfunction

Presenter: Mariam Lawani, Medical Student

Research Interest: Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: Alison Morris MD, MS, Meghan Fitzpatrick MD

Funding Source: R01 125049

Authors: Mariam Lawani BSc, Meghan Fitzpatrick MD, Heather Michael BS, Abbe De Vallejo PhD, Lawrence Kingsley DrPH, Alan Landay PhD, Laurence Haung MD, Alison Morris MD, MS

Introduction: HIV infection is an independent risk factor for pulmonary dysfunction. Clonally expanded CD8 T-cells persist throughout HIV infection and are characterized by T-cell exhaustion and senescence, which are associated with non-AIDS co-morbidities like chronic obstructive pulmonary disease (COPD). Whether exhaustion and senescence represent distinct mechanistic processes in HIV-associated lung disease has not been studied.

Methods: HIV+ participants performed standardized pulmonary function tests. PBMCs were phenotyped by flow-cytometry for T-cell memory subset distribution, markers of exhaustion [PD1] and replicative senescence [CD28-CD57+]. Correlations between T-cell markers and airway obstruction measured by post-bronchodilator forced expiratory volume in 1 second (FEV1) and/or FEV1/forced vital capacity (FVC) were made and adjusted for smoking.

Results: 63 HIV+ participants were enrolled; 92% were on ART; 75.6% were virologically-suppressed. Mean age was 50.6 years, 23.8% were female and 75% had a smoking history. Overall, depletion of the CD4 naïve compartment and increased frequency of the CD8 TEMRA subset trended with worse airflow obstruction (data not shown). PD1 upregulation on naïve CD8 T cells was associated with worse airflow obstruction [FEV1/FVC β=-0.35 p=0.001]. Increased frequencies of senescent naïve CD8 T cells were also associated with worse airflow obstruction [FEV1/FVC β=-0.12 p=0.02]. However, PD1 upregulation on naïve CD8 T cells was inversely related to %predicted FEV1 [β=-0.55, p=0.03], no association was seen in senescent naïve CD8 T cells.

Conclusion: Upregulation of senescent and exhaustion markers are associated with aspects of HIV-COPD. Expression of senescent and exhaustion markers are not always correlated, supporting the evidence of independent induction of these mechanisms in HIV-associated lung disease.
**90-A Poster:** Lymphocyte Memory Subset Activation and Senescence are Associated with Pulmonary Dysfunction in HIV-Infected Individuals

**Presenter:** Mariam Lawani, Medical Student  
**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD, MS, Meghan Fitzpatrick MD  
**Funding Source:** NIH K24 HL123342, R01 HL120398 (AM)

**Authors:** Mariam Lawani BSc, Meghan Fitzpatrick MD, Cathy Kessinger RN, Nicolas Leo BS, Abbe De Vallejo PhD, Karen Norris MD, Alan Landay PhD, Alison Morris MD, MS

**Introduction:** HIV is an independent risk factor for pulmonary dysfunction. Both HIV and COPD are independently associated with chronic inflammation, senescence, and immune activation. Limited reports in HIV-COPD have described associations of activated-senescent T-cell phenotypes and pulmonary function testing (PFT) abnormalities, but comparisons to uninfected persons have not been made. Additionally, abnormal lymphocyte memory subset redistribution is associated with chronic inflammation; memory subsets have not been evaluated in the context of HIV-associated pulmonary dysfunction. We compared surface markers of lymphocyte activation and senescence and proportions of lymphocyte memory subsets to PFTs in HIV-infected and uninfected persons.

**Methods:** HIV-infected and uninfected persons were recruited from an outpatient cohort. Clinical factors including demographics, smoking exposure, and measures of HIV viral control were collected. Participants performed ATS standard PFTs. Peripheral blood mononuclear cell lymphocytes were analyzed by flow cytometry for expression of activation (CD38+, HLA-DR+, CD69+), senescence (CD28 nullCD57+), and memory subsets (naive[CD4+CD45RA+CCR7+], central memory [TCM CD4+CD45RA-CCR7+], effector memory [TEM CD4+CD45RA-CCR7-] and terminally differentiated [TEMRA CD4+CD45RA-CCR7-]). Relationships between T-cell markers and PFTs were tested by Spearman's correlation, t-test, or rank-sum. Regression was used to adjust for clinically relevant variables.

**Results:** 79 participants were enrolled, of whom 60 (77%) were HIV-infected. Mean age of participants was 49.5 years. HIV-infected individuals had a greater smoking history than HIV-uninfected (median pack-years 16.87 vs. 0.15, p=0.01). 95% of HIV-infected persons used ART (median CD4 567.5 cells/mm3, range [3-1619]; median viral load 43, range [UD-78771]). PFTs were normal on average, but 16.9% had post-bronchodilator FEV1/FVC<0.7 and 55.7% had DLCO < 0.8. There were no significant differences in PFTs by HIV status in this cohort.Certain activated and senescent phenotypes (CD38+/CD8+, CD38+/CD28nullCD57+/CD8+, CD28nullCD57+/CD8+/CD69+/CD4+, CD38+/CD28nullCD57+/CD4+, CD69+/CD28nullCD57+/CD4+) were more frequent among HIV-infected (not shown). Higher proportions of naive CD8 T-cells independently correlated with better DLCO (beta = 0.37, p = 0.007), and higher proportions of CD4 TEMRA were independently associated with greater odds of post bronchodilator FEV1<0.8 (OR 3.5 [95%CI:1.4-9.2, p=0.01]) in HIV-infected persons only. Higher CD69+/CD8+ expression independently associated with post-bronchodilator FEV1/FVC<0.7 (OR 6.3 [95% CI: 1.2-33.3, p=0.03]), and higher CD28nullCD57+/CD4+ expression associated with lower post-bronchodilator FEV1percent-predicted (beta = -0.03, p=0.03) in HIV-infected persons.

**Conclusion:** Results are consistent with prior findings that upregulation of senescent and immune activation markers are associated with lung dysfunction in HIV. Lymphocyte memory compartments may be novel important markers of T-cell immunopathogenesis in HIV-associated lung dysfunction.
**91-A Poster:** Townes sickle cell mouse model exhibit structural and functional cardiac features consistent with human sickle cell disease

**Presenter:** Maureen Mburu, Post-Doctoral Fellow  
**Research Interest:** Translational Cardiology

**Mentors:** Flordeliza Villanueva MD, Solomon Ofori-Acquah PhD  
**Funding Source:** T32

**Authors:** Maureen Mburu MD, Rafey Feroze BS, Xucai Chen PhD, Daniel Whitehurst BS, Solomon Ofori-Acquah PhD, Flordeliza Villanueva MD

**Introduction:** Cardiopulmonary complications are the leading cause of mortality in patients with sickle cell disease (SCD), for which effective therapies are lacking. Transgenic murine models of SCD have proven useful in studying mechanisms of SCD complications, such as acute chest syndromes, and therefore offer an important means to identify potential pathophysiologic approaches for new treatments. Little is known, however, of the natural history of cardiac disease in these models and hence their utility for studying cardiovascular complications of SCD. We hypothesize that echocardiography can be used to characterize the structural and functional properties of the hearts of transgenic mice with SCD.

**Methods:** We studied Townes sickle cell mice homozygous for human SS hemoglobin, which develop hemolytic anemia. Control mice were heterozygous AS, which do not develop anemia. 2D echocardiography was performed using high frequency ultrasound in cohorts of mice at 1 (n=4 SS and 4 AS) and 6 months (n= 3 SS and 2 AS) of age. Standard indices of left ventricular (LV) systolic function, size, and mass, were derived from measurements made on short-axis images of the heart.

**Results:** SS mice had significantly higher LV mass and cardiac output compared to controls at 1 and 6 months. At 6 months, SS mice had higher LV internal diameter (p=0.02), diastolic volume (p=0.02), and stroke volume (p=0.05) compared to AS controls. Ejection fraction and fractional shortening were similar for AS and SS mice at both time points. Within the SS group, there was a higher LV mass (p=0.009), cardiac output (p=0.03) and stroke volume (p=0.04) at 6 months compared to 1 months.

**Conclusion:** We have echocardiographically demonstrated progression of LV enlargement and dilation in Townes SS mice compared to control mice, and as a function of age, with preservation of LV systolic function. This model displays a similar cardiac phenotype to that found in patients SCD and thus may be useful for pathophysiologic study of SCD-associated cardiac complications.
**Introduction:** Cigarette smoking accelerates aging. However, the molecular pathways responsible for cigarette smoke (CS)-induced cellular senescence are not fully elucidated. We hypothesize that some gene expression patterns altered by acute cigarette smoke exposure may contribute to the development of cellular senescence.

**Methods:** Primary human bronchial epithelial cells obtained from five healthy patients were cultured and either treated with or without 1.5% CS extract (CSE) for 24 h. Then, total RNA samples were extracted from both of these conditions. A third sample was taken when non-CSE exposed cell cultures were determined to have reached replicative senescence. These samples were sequenced on an Illumina HiSeq 200 Genome Analyzer.

**Results:** Using RNA-Seq, mRNA was analyzed from both a senescent and CSE-exposed conditions. In total, 1,892 genes were found to be differentially regulated, 1,529 during senescence, 599 in after CSE-exposure, with 243 of these genes in both conditions. The gene sets enriched in both conditions belonged to cellular processes that regulate reactive oxygen species, proteasome degradation and NF-κB signaling.

**Conclusion:** Coordinate regulation of a multitude of genes during aging and CSE occur that may provide molecular insight into cellular senescence.
**93-A Poster:** NNRTI-CONTAINING ART IS EFFECTIVE FOR DAPIVIRINE RING BREAKTHROUGH HIV-1 INFECTION

**Presenter:** Amy Opest, Junior Faculty Research Interest: Translational
Infectious Diseases

**Mentors:** None Funding Source: DAIDS

**Authors:** Sharon Riddler MD, Jennifer Balkus PhD, Amy Opest MS, John Mellors MD, Urvi Parikh PhD, Carolyn Akello MD, Sufia Dadabhai PhD, MHS, Felix Mhlanga PhD, Colin O'Rourke, Jared Baeten MD

---

**Introduction:** A vaginal ring containing dapivirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), was safe and effective in preventing HIV-1 infection in African women. Among women who acquired HIV-1 infection during the ASPIRE study conducted by the Microbicide Trials Network (MTN-020), NNRTI resistance associated mutations were detected in both dapivirine ring and placebo ring recipients with no significant difference between arms. NNRTI-based antiretroviral therapy (ART) remains the first-line standard of care in many regions of the world. The impact of dapivirine ring use at the time of HIV-1 acquisition on the subsequent response to NNRTI-containing ART is unknown.

**Methods:** The virologic failure rate following initiation of ART was assessed among women who acquired HIV-1 infection during participation in MTN-020, a randomized, placebo-controlled trial of a monthly dapivirine vaginal ring. Virologic failure was defined as lack of suppression of plasma HIV-1 RNA to <200 copies/ml by 6 months after ART initiation or viral rebound to ≥200 copies/ml after initial suppression at any time.

**Results:** Among 168 participants with incident HIV-1 infection during dapivirine or placebo ring use in MTN-020, 158 (94%; 65 dapivirine, 93 placebo) had at least 1 follow-up visit, of whom 78 (49%) initiated NNRTI-containing ART during follow-up (29 dapivirine, 49 placebo). The median time from estimated HIV-1 seroconversion to ART initiation was 10.3 months. The median time from ART initiation to HIV-1 RNA <200 copies/ml was approximately 90 days for both dapivirine and placebo ring recipients. The Cox proportional hazards model estimate for the likelihood of virologic suppression between the dapivirine ring and placebo ring arms was 1.0 (95% confidence interval 0.6-1.6). Among 57 women with at least 6 months of post-ART follow-up, 10 (17.5%) experienced virologic failure, 6/36 (16.7%) placebo ring recipients and 4/21 (19%) dapivirine ring recipients (P=0.82).

**Conclusion:** Compared to placebo, we observed no difference in the time to virologic suppression or the risk of virologic failure for women who had received the dapivirine vaginal ring and then initiated NNRTI-containing ART. These results provide reassurance that standard WHO-recommended ART regimens are effective in the setting of breakthrough HIV-1 infection in women who had received the dapivirine vaginal ring, although continued monitoring of virologic response is warranted.
**Introduction:** 50,000 suffer from carbon monoxide (CO) poisoning every year in the United States alone. Even with current therapeutic options, a significant amount of moderate to severe CO poisoning is complicated by cardiac dysfunction which is associated with increased long-term mortality. Up to 40% of survivors will suffer from permanent neurocognitive deficits. CO toxicity is mediated by: (1) CO binding to hemoglobin, decreasing global oxygen delivery and (2) CO binding to cytochrome c oxidase in the electron transport chain, inhibiting mitochondrial respiration. The shutdown of oxidative phosphorylation reduces cellular energy availability and causes free oxygen radical generation. We have developed a recombinant neoglobin (rNgb) that has a high affinity for CO that chelates CO directly from hemoglobin and cytochrome c oxidase.

**Methods:** We measured mitochondrial respiration using a Clark-type oxygen electrode respirometry system. We obtained left ventricle tissue homogenate from healthy rats. We added substrates (adenosine disphosphate, pyruvate and malate) to maximize tissue respiration until hypoxia. We then compare respiration rates after reoxygenation in tissue exposed to 99.9% CO gas, to CO gas then rNgb, to rNgb without CO exposure, and control. Separately, we exposed sedated, ventilated mice to 4.5 minutes of 30,000 parts per million CO. After poisoning, we infused either phosphate buffered saline (PBS) or rNgb. We isolated heart tissue after the exposure experiment and measured maximal tissue respiration using the same respirometry system. We compared the respiration rate of these poisoned mice (PBS and rNgb) between each other and to mice that were sedated but not exposed to CO.

**Results:** In vitro, CO inhibited respiration rate by 33.0% (+/- 5.9%) compared to control rate. Control and rNgb without CO did not affect the respiration. The addition of rNgb reversed CO-dependent inhibition of respiration (two-way ANOVA for exposure (CO or rNgb), P<0.0001, and interaction of the two, P<0.0001). In vivo, severely CO-poisoned mice had respiration of heart tissue that was 62.3% (+/- 7.5%) of sedated control mice (unpaired t-testing, P=0.0148). Treatment with rNgb restored tissue respiration rate to the level of control and significantly higher than the rates of mice treated with PBS (P=0.0366).

**Conclusion:** CO scavenging through the use of our agent, rNgb, can reverse CO-induced tissue respiration inhibition both in vitro and in vivo. Through restoration of tissue respiration, CO scavenging may serve as an antidote for CO poisoning.
95-A Poster: Modified mesenchymal stem cells using miRNA transduction modifies inflammation and collagen deposition in lung fibrosis

Presenter: Jacobo Sellares, Junior Faculty

Research Interest: Translational Pulmonary, Allergy and Critical Care Medicine

Mentors: Mauricio Rojas MD

Funding Source: R01

Authors: Jacobo Sellares MD, Luai Huleihel PhD, Nayra Cardenes PhD, Diana Alvarez MD, Rosa Faner PhD, Koji Sakamoto PhD, Guoying Ju PhD, Maria G Patanaki PhD, Naftali Kaminski MD, Mauricio Rojas MD

Introduction: Although different preclinical models have demonstrated a favorable role of bone marrow derived-mesenchymal stem cells (B-MSCs) in preventing fibrosis, this protective effect is not observed with late administration of B-MSCs, when fibrotic changes are consolidated. The possibility of modify B-MSCs to prevent deleterious effects or even enhancing their therapeutic properties could be relevant in their future potential therapeutic use. We sought out to investigate if the modification of B-MSCs using miRNAs let-7d (antifibrotic) and miR-154 (profibrotic) could modify their ability to alter lung fibrosis in a murine bleomycin model

Methods: Concentrated let-7d, miR-154 miRNAs or a control sequence lentiviral vector were transduced into human B-MSCs. These modified B-MSCs were intravenously administered to mice at day 7 day after bleomycin instillation. Mice were sacrificed at day 14. Different epithelial/mesenchymal markers in B-MSCs were assessed. In addition, the effect of modified B-MSCs in physical signs and diferent lung fibrosis markers on mice were also evaluated

Results: B-MSCs were successfully modified and overexpressed let-7d and miR-154 after transfection. Although no reverse in lung fibrosis was observed, bleomycin-injured animals that were treated with let7d- B-MSCs were found to have an improvement in weight and a reduction in collagen mRNA levels in lung tissue, what suggests a decrease in activity of lung fibrosis progression. This positive effect was probably associated with the changes of B-MSCs epithelial/mesenchymal properties after miRNA modification. Treatment with miR154 modified-BMSCs not only did not have a beneficial effect but miR-154 group had the worst survival.

Conclusion: Our results establish the use of modified B-MSCs with mi-RNAs as a potential future treatment in lung fibrosis.
Introduction: The optimal timing, level, and route of delivery of caloric support in critically ill patients with sepsis remain unclear. Animal models of sepsis provide valuable insight on the mechanistic implications of early nutritional therapy. Prior work in our lab has demonstrated that early low level enteral dextrose initiated in the acute phase of sepsis has beneficial effects on glucose metabolism and inflammation in mouse models. We hypothesize that the therapeutic effects of enteral dextrose are mediated by the intestinal-derived incretin hormones GIP and GLP-1 that stimulate insulin secretion in response to enteral nutrients.

Methods: In an initial set of experiments to test the effects of continuous enteral dextrose on incretin release, 10 week old C57BL/6J mice (n=12) were administered lipopolysaccharide (LPS) challenge (1 mg/kg) followed by either (1) low level enteral dextrose infusion (equivalent to 10% daily caloric needs) or (2) enteral saline. Plasma incretin levels were measured five hours after initiation of dextrose infusion. In a second set of experiments to test the role of the incretin pathway, endotoxemic C57BL/6J mice receiving enteral dextrose (n=12) were randomized to receive either (1) pharmacologic incretin blockade or (2) vehicle. Frequently sampled intravenous glucose tolerance test (FSIVGTT) was performed five hours after septic insult to determine metabolic function. Plasma cytokine levels were measured with the BioRad 23-Plex Mouse Cytokine Multiplex Assay.

Results: Enteral dextrose infusions increased levels of the incretin hormone GIP (332 ± 99 vs 76 ± 12 pg/mL, p = 0.02) but did not increase levels of GLP-1 (p=0.31) compared to saline controls. Blockade of GIP signaling with the competitive GIP antagonist 3ProGIP (Bachem Americas) abrogated the beneficial effects of enteral dextrose in endotoxemic mice by worsening glucose disposal (area under the glucose curve: 28150 [GIP blocker] vs. 8378 mg*min/dL [vehicle], p<0.01), blunting insulin release (acute insulin response: 158 [GIP blocker] vs. 1042 µU/mL [vehicle], p<0.01), and dramatically increasing release of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-a (p<0.01 for all).

Conclusion: Enteral dextrose has beneficial effects on insulin release, glucose metabolism, and pro-inflammatory cytokine levels in an endotoxemic model associated with increases in the incretin hormone GIP which stimulates insulin release. Pharmacologic blockade of the GIP pathway abolishes the beneficial effects of enteral dextrose in this model. Future studies will explore the impact of nutrition strategies on increasing incretin hormone release to improve outcomes in septic patients.
97-A Poster: A universal Sequential Dual-Receptor-targeted Pre-Targeting (SDRPT) strategy for immuno-PET

Presenter: Lingyi Sun, Post-Doctoral Fellow Cardiology

Research Interest: Translational

Mentors: Dexing Zeng PhD

Funding Source: NIH R21-EB017317, R21-EB020737

Authors: Lingyi Sun PhD, Yongkang Gai PhD, Xiaohui Zhang PhD, Dexing Zeng PhD

Introduction: Immuno-PET is like performing “comprehensive immunohistochemical staining in vivo”, by using radiolabeled monoclonal antibody (mAb). Due to the wide availability and extraordinary binding affinity/specificity of mAbs, immuno-PET has been considered as a highly promising approach for molecular imaging of various diseases. However, its application in heart and vascular diseases was limited by the high non-specific uptakes (particular in blood). In order to overcome those concerns, we developed a universal (SDRPT) strategy, by sequential administrating a TCO-modified mAb (TCO-mAb) and a Tz-modified fast-clearing targeting-ligand labeled with a short half life time radioisotope (Tz-RM-TL). Herein, TCO/Tz is a pair of bioorthogonal ligation moieties that covalently ligate in a close proximity.

Methods: In our proof of principle study, SDRPT was validated by the PET imaging of human-EGFR expression in mice bearing both EGFR+ and EGFR- xenografts. EGFR is a versatile signaling pathway integrator associated with vascular homeostasis and diseases. In particular, TCO-cetuximab was administrated and allowed to accumulate on EGFR+ xenograft along with the concomitant blood clearance for 24h. Sequentially, Tz-NOTA (Cu64)-RGD was administrated (RGD has been used for PET imaging of vascular imaging diseases in human) PET imaging was conducted at various post-injection time points (4h, 18h, 28h, and 48h post injection), and the results were compared to the traditional immune PET strategy using (64Cu)-cetuximab.

Results: Compared to the traditional immuno-PET using (64Cu)-cetuximab, our SDRPT PET showed greatly enhanced signal/noise ratios (e.g., xenograft/blood, xenograft/liver, xenograft/heart) at all time points examined. The maximum signal to background ratio was obtained at 18h, in which xenograft/blood was 10.5 ± 1.2 while that of the traditional immuno-PET using ((64Cu)-cetuximab was only 1.8 ± 0.47. In the human-EGFR- xenograft, tumor uptake of Tz-(64Cu)NOTA-RGD dropped from 2.3 ± 0.21 ID%/g at the early time point (4h) to 0.3 ± 0.1 ID%/g at 18h p.i., which was only one thirtyth of that in human-EGFR+ xenograft. Therefore, the fast clearing Tz-(64Cu)NOTA-RGD did not exhibit a long time tumor retention, and the high uptake observed in human-EGFR+ xenograft was correlated to the overexpressed EGFR.

Conclusion: The developed SDRPT PET imaging technology demonstrated a great potential on PET imaging of human-EGFR expression in xenograft model with an exceptional signal/noise ratios. Therefore, our SDRPT PET imaging can overcome the limitations in current immuno-PET, and consequently benefiting the in vivo imaging of heart and vascular diseases especially when the small molecule imaging probe for the biomarker of interest is not available.
**Introduction:** PET has been served as a clinical tool for non-invasive imaging of various diseases, including heart-vascular disease, cancer and central nervous disorders. Due to the avidity effects (e.g., enhanced affinity, increased targeting-receptors, and possibly improved pharmacokinetics), heterodimerization has emerged as a promising strategy to improve in vivo performance compared to the monomer counterparts. Among various cardiac angiogenesis targets, integrin-avß3 and CD13 has been extensively investigated, and the integrin-avß3 targeted RGD peptide has been used for PET imaging of angiogenesis in patients with atherosclerosis, myocardial infarction, etc. while the CD13-targeted NGR peptide has been applied in the selective imaging of cardiac angiogenesis by various research group. In this project, we developed the avß3-CD13 dual targeted heterodimer (RGD-NOTA-NGR) to further enhance specific uptake and increase signal/noise ratios thus facilitating the in vivo PET imaging of cardiac angiogenesis.

**Methods:** RGD-NOTA-NGR heterodimeric ligand was prepared via the metal-free click reaction using our recently developed bifunctional chelator (COOH-NOTA-N3). To demonstrate its superiority to the monomer counterparts, the prepared heterodimer was then labeled with Ga-68 for in vivo evaluation on mice bearing BxPC3 xenografts overexpressing both integrin avß3 and CD13, and the resulting PET images were compared to those obtained from two corresponding Ga-68 labeled monomers in the same animal model. All PET images were acquired at 1 h post-injection, and the mice were scarified immediately for ex vivo biodistribution studies.

**Results:** RGD-NOTA-NGR heterodimer was prepared from the commercially available RGD and NGR peptides in 6 steps with 15% overall synthetic yield. At 70 °C, Ga-68 radiolabeling of the resulting RGD-NOTA-NGR was completed in 15 mins with a labeling yield above 95% at a specific activity of 1.0 mCi/nmole. Without further purification, 200 µCi of RGD-(68Ga)-NGR were injected for in vivo evaluation in the BxPC3 xenograft mouse model. The resulting PET images indicated that the heterodimer exhibited the highest signal to noise ratio, compared to the other two monomeric PET tracers. The quantitative region of interest (ROI) analysis revealed that the xenograft uptake of the RGD-(68Ga)-NGR (1.6%ID/g) was much higher than that of monomeric RGD (1.2%ID/g) and NGR (0.8%ID/g). In post-imaging ex vivo biodistribution studies, the RGD-NGR dimer exhibited high signal/noise ratios (xenograft/blood and xenograft/muscle ratios were 25 and 15, respectively).

**Conclusion:** A heterodimeric RGD-NGR PET tracer for angiogenesis imaging has been successfully developed in this project, and preliminary results demonstrated its great potential for being applied in PET imaging of cardiac angiogenesis.
99-A Poster: Epigenetic and genetic silencing of the iron-sulfur cluster scaffold protein BOLA3 drives pulmonary vascular proliferation and vasoconstriction

Presenter: Qiujun Yu, Post-Doctoral Fellow Cardiology
Research Interest: Translational Cardiology

Mentors: Stephen Chan MD, PhD
Funding Source: RO1

Authors: Qiujun Yu PhD, Miranda Tai MS, Joseph Chen BS, Ying Tang MS, Stephen Chan MD, PhD

Introduction: Iron-sulfur clusters [Fe-S] are essential bioactive metal complexes that control cellular redox state and mitochondrial metabolism. Multiple mitochondrial dysfunction syndrome (MMDS), a fatal and rare autosomal recessive disorder of systemic energy metabolism, has been linked to mutations in the [Fe-S] scaffold gene BOLA3. However, the role of BOLA3 in pulmonary vascular function remains unclear. This study is aimed at investigating whether loss of BOLA3, either from genetic or hypoxic triggers, contributes to alterations of mitochondrial metabolism and pulmonary arterial endothelial dysfunction, thus predisposing to the development of PH.

Methods: In human pulmonary artery endothelial cells (hPAECs), mitochondrial oxygen consumption, glycolytic flux, and proton leak were analyzed by Seahorse assay. Mitochondrial O2-production were measured via Mitosox labeling. In vitro angiogenesis was assessed by tube formation in matrigel, and apoptosis was measured by caspase-3/9 activity assay. Chromatin immunoprecipitation coupled with quantitative PCR (ChIP-qPCR) was performed to analyze enrichment of acetylated histone at the BOLA3 promoter.

Results: In cultured hypoxic hPAECs as well as lung tissues from multiple rodent models of PH, endothelial BOLA3 expression was downregulated. Immunohistochemistry also revealed reduced expression of BOLA3 in pulmonary vascular endothelium of PH patients and rat lungs of monocrotaline-induced PH. A histone deacetylase inhibitor, Scriptaid, reversed hypoxia-induced BOLA3 silencing, whereas inhibitors of BET protein bromodomains, conserved protein modules that recognize acetylated lysine residues and carry histone acetyltransferase activities, inhibited BOLA3 expression under normoxia. ChIP-qPCR demonstrated that hypoxia decreased epigenetic histone 3 lysine 9 acetylation at the BOLA3 promoter. siRNA-mediated BOLA3 knockdown compromised Fe-S integrity and inhibited expression and activity of critical components of mitochondrial oxidative metabolism, including lipoate-containing pyruvate dehydrogenase, a-ketoglutarate dehydrogenase, and respiratory chain complexes I and II. More importantly, glycolytic influx in hypoxic hPAEC was increased by BOLA3 inhibition while mitochondrial oxygen consumption elevated accompanied by increased proton leak of the electron transport chain and mitochondrial O2-production. Transfection of hPAECs with lentiviral vectors expressing the mitochondrial, but not the cytosolic isoforms of BOLA3 restored mitochondrial integrity and metabolism. As a result, siRNA knockdown of BOLA3 inhibited apoptosis and angiogenic potential, while promoting endothelial cell dependent smooth muscle cell contraction.

Conclusion: BOLA3 is epigenetically regulated by hypoxia and carries essential roles in PAECs in the production of [Fe-S] clusters for the maturation of lipoate-containing 2-oxoacid dehydrogenase and the assembly of respiratory chain complexes. Consequently, silencing of BOLA3 promotes metabolic re-programming hence a pro-proliferative and vasoconstricted pulmonary vascular state.
**Poster Abstracts**

**100-A Poster:** Relaxin reverses fibrosis and rescues the bladder in mice with chronic radiation cystitis

**Presenter:** Irina Zabbarova, Junior Faculty  
Renal-Electrolyte

**Research Interest:** Translational

**Mentors:** Anthony Kanai PhD  

**Funding Source:** NIH NIDDK

**Authors:** Youko Ikeda PhD, F. Aura Kullmann PhD, Bronagh McDonnell PhD, Lori Birder PhD, Guy Salama PhD, Anthony Kanai PhD

**Introduction:** Fibrosis has been implicated as a mechanism in a variety of pathologies including lower urinary tract dysfunction due to chronic radiation cystitis, where symptoms include decreased bladder compliance and force generation leading to urinary retention. Patients may need intermittent self-catheterization or a cystectomy as there are presently no effective therapies that reverse fibrosis. We developed a model of radiation cystitis in mice that obtain fibrotic bladders within seven weeks, and tested the therapeutic benefits of the antifibrotic hormone, relaxin, currently in phase 3 clinical trials for treating acute decompensated heart failure.

**Methods:** Adult female C57BL/6 mice were anesthetized (avertin, 5 mg/kg), a lower midline incision made and the urinary bladder externalized for selective irradiation (10 Gray, 1 Gy = 100 rad; X-RAD 320 KV). Seven weeks later, osmotic pumps were implanted subcutaneously at the lower back of mice to deliver saline or relaxin at 400 µg/kg/day/14 days. Following treatment, voiding function was evaluated using decerebrate cystometrograms (CMGs), external urethral sphincter (EUS) electromyograms (EMGs) and urine spot analyses. Bladder contractility was assessed using length-tension measurements, Cav1.2 and relaxin receptor 1 & 2 expression using immunofluorescence and bladder wall fibrosis using histology.

**Results:** These studies are the first to show relaxin receptor expression (1 & 2) in the bladder and that treatment with human relaxin reversed bladder fibrosis. CMG and EUS-EMG recordings revealed overflow incontinence in untreated irradiated mice due to decreased compliance and force generation and a prolonged EUS guarding reflex. In treated mice, CMG and EUS-EMG recordings were similar to those in non-irradiated mice. Urine spot patterns showed that non-irradiated mice void in one area of the cage demonstrating continence, while irradiated animals leak exhibiting incontinence as early as two weeks following irradiation and develop retention with time. Relaxin treated mice exhibited normal voiding patterns as controls. Stained tissue sections from irradiated mice showed loss of the urothelium, increased collagen content and significant muscle damage nine weeks post injury while treated mice showed a return of the urothelium and normal collagen and smooth muscle architecture.

**Conclusion:** These studies demonstrate that relaxin can reverse fibrosis and treat irradiation-induced bladder dysfunction when administered after the insult. Relaxin treatment decreases passive and increases active tension profiles in isolated bladder sheets. The increase in active tension is due, in part, to decreased collagen content and increased Cav1.2 expression. This treatment also inhibits inflammation permitting the urothelium to recover and reestablish barrier function.
Session B

May 2, 2017
Biomedical Science Tower Foyer
<table>
<thead>
<tr>
<th><strong>SESSION B</strong></th>
<th><strong>May 2, 2017</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acharya</strong></td>
<td>Runa 27-B</td>
</tr>
<tr>
<td></td>
<td>The Utility of Adrenal Venous Sampling for Guiding Surgical Management in Patients with Bilateral Adrenal Enlargement and ACTH-independent Cushing’s Syndrome</td>
</tr>
<tr>
<td><strong>Agustin</strong></td>
<td>J. Cruz 1-B</td>
</tr>
<tr>
<td></td>
<td>IL-17 signaling inducibly degrades ABIN1, a constitutive inhibitor of inflammatory signaling</td>
</tr>
<tr>
<td><strong>Ali</strong></td>
<td>Hira 28-B</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia and clinical outcomes at one year in non-critically ill hospitalized patients with diabetes</td>
</tr>
<tr>
<td><strong>Allenbaugh</strong></td>
<td>Jill 67-B</td>
</tr>
<tr>
<td></td>
<td>A communication intervention aimed at medicine doctors and nurses improves patient satisfaction scores</td>
</tr>
<tr>
<td><strong>Allsup</strong></td>
<td>Kelly 29-B</td>
</tr>
<tr>
<td></td>
<td>Stratification of Patients in Cardiac Rehabilitation as Novel Programs Develop</td>
</tr>
<tr>
<td><strong>Amatya</strong></td>
<td>Nilesh 2-B</td>
</tr>
<tr>
<td></td>
<td>Post-transcriptional regulation of IL-17-dependent signal transduction</td>
</tr>
<tr>
<td><strong>Bain</strong></td>
<td>William 76-B</td>
</tr>
<tr>
<td></td>
<td>Identification of a region within the Thrombospondin-1 Type III Domain with inhibitory activity against P. aeruginosa elastase activity</td>
</tr>
<tr>
<td><strong>Bhattacharya</strong></td>
<td>Saveri 77-B</td>
</tr>
<tr>
<td></td>
<td>Alterations in the β-catenin pathway in non-small cell lung cancer defines a distinct molecular subtype with prognostic and therapeutic implications</td>
</tr>
<tr>
<td><strong>Boeckman</strong></td>
<td>Jennifer 31-B</td>
</tr>
<tr>
<td></td>
<td>Follicular Lymphoma as the Presenting manifestation of Common Variable Immune deficiency in an Adult Patient</td>
</tr>
<tr>
<td><strong>Bungo</strong></td>
<td>Christina 32-B</td>
</tr>
<tr>
<td></td>
<td>Antibiogram-a-rama: Comparing Antibiograms to Guide Providers in the Treatment of UTI</td>
</tr>
<tr>
<td><strong>Bungo</strong></td>
<td>Christina 33-B</td>
</tr>
<tr>
<td></td>
<td>You’re Fired, Fluoroquinolones!</td>
</tr>
<tr>
<td><strong>Byard</strong></td>
<td>Thomas 34-B</td>
</tr>
<tr>
<td></td>
<td>Impact of Depression or Anxiety on Enrollment in Cardiac Rehabilitation in Veterans</td>
</tr>
<tr>
<td><strong>Carter</strong></td>
<td>Andrea 68-B</td>
</tr>
<tr>
<td></td>
<td>Resident Experiences with a Program to Support Academic Scholarship during Internal Medicine Residency Training</td>
</tr>
<tr>
<td><strong>Chen</strong></td>
<td>Ting-Yun 4-B</td>
</tr>
<tr>
<td></td>
<td>Characterization of Putative Promoters in the Human RXFP1 Gene</td>
</tr>
<tr>
<td><strong>Choi</strong></td>
<td>Jaeyeon 35-B</td>
</tr>
<tr>
<td></td>
<td>A novel neutrophil-specific PET probe targeting formyl peptide receptor type 1: 64Cu-NODAGA-PEG12-cBLCLF</td>
</tr>
<tr>
<td>Author</td>
<td>Name</td>
</tr>
<tr>
<td>-------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Chuan</td>
<td>Byron</td>
</tr>
<tr>
<td>Click</td>
<td>Benjamin</td>
</tr>
<tr>
<td>Culley</td>
<td>Miranda</td>
</tr>
<tr>
<td>Desai</td>
<td>Aken</td>
</tr>
<tr>
<td>Dowlatshahi</td>
<td>Samaneh</td>
</tr>
<tr>
<td>Eaton</td>
<td>Amity</td>
</tr>
<tr>
<td>Edem</td>
<td>Dinesh</td>
</tr>
<tr>
<td>Eden</td>
<td>Elizabeth</td>
</tr>
<tr>
<td>Elliott</td>
<td>Andrea</td>
</tr>
<tr>
<td>Erqou</td>
<td>Sebhat</td>
</tr>
<tr>
<td>Eshbach</td>
<td>Megan</td>
</tr>
<tr>
<td>Evankovich</td>
<td>John</td>
</tr>
<tr>
<td>Evans Phillips</td>
<td>Anna</td>
</tr>
<tr>
<td>Evans Phillips</td>
<td>Anna</td>
</tr>
<tr>
<td>Name</td>
<td>Last Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Farkas</td>
<td>Amy</td>
</tr>
<tr>
<td>Fridman</td>
<td>Yaron</td>
</tr>
<tr>
<td>Gauthier</td>
<td>Marc</td>
</tr>
<tr>
<td>Genuardi</td>
<td>Michael</td>
</tr>
<tr>
<td>Giacobbi</td>
<td>Nicholas</td>
</tr>
<tr>
<td>Haidar</td>
<td>Ghady</td>
</tr>
<tr>
<td>Haidar</td>
<td>Ghady</td>
</tr>
<tr>
<td>Hemraj</td>
<td>Alisha</td>
</tr>
<tr>
<td>Hernandez</td>
<td>Gerard</td>
</tr>
<tr>
<td>Huckestein</td>
<td>Brydie</td>
</tr>
<tr>
<td>Istvanic</td>
<td>Filip</td>
</tr>
<tr>
<td>Jakubowski</td>
<td>Karen</td>
</tr>
<tr>
<td>Jang</td>
<td>Sae</td>
</tr>
<tr>
<td>Jantea</td>
<td>Rachel</td>
</tr>
<tr>
<td>Kellar</td>
<td>Garrett</td>
</tr>
<tr>
<td>Author</td>
<td>Title</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kinsman</td>
<td>OVLT Neuron Responses to Hypertonic NaCl and Mannitol Differ: Implications for Neural Regulation of Blood Pressure by NaCl</td>
</tr>
<tr>
<td>Kitsios</td>
<td>Dysbiosis Associated With The Acute Respiratory Distress Syndrome: A Prospective Cohort Study in Adults</td>
</tr>
<tr>
<td>Kitsios</td>
<td>Microbial Dysbiosis In Sepsis and Associated Clinical Outcomes</td>
</tr>
<tr>
<td>Kitsios</td>
<td>The Microbiome in Lung Explants of Idiopathic Pulmonary Fibrosis (MiLEs-IPF): a case-control study in patients with end-stage fibrosis</td>
</tr>
<tr>
<td>Lear</td>
<td>Chemical Inhibition of DCUN1D1, a New Approach of Targeting Cullin Neddylation for Lung Cancer Treatment</td>
</tr>
<tr>
<td>Levine</td>
<td>Development of a Severe Rat Model of Metabolic Syndrome, Pulmonary Hypertension, and Heart Failure with Preserved Ejection Fraction (PH-HFpEF)</td>
</tr>
<tr>
<td>Liou</td>
<td>Vascular Endothelial Growth Factor May Impair Pro-Chondrogenic Activity of Platelet-Rich Plasma on Human Adipose Stem Cells</td>
</tr>
<tr>
<td>Lusica</td>
<td>Hypoglycemic Episodes in ICU patients on glucose containing Prismsate CRRT compared to non-glucose containing Phoillum CRRT</td>
</tr>
<tr>
<td>Martin</td>
<td>Relaxin Reduces Inflammatory Gene Expression in Aged Rats</td>
</tr>
<tr>
<td>Masri</td>
<td>Outcomes of Heart Failure Admissions under Observation versus Short Inpatient Stay</td>
</tr>
<tr>
<td>Masri</td>
<td>Persistent Pulmonary Hypertension following Transcatheter Aortic Valve Replacement Is Common and Associated with Higher Mortality</td>
</tr>
<tr>
<td>Masri</td>
<td>Tc-99m PYP Scan for Cardiac Amyloidosis: Will a Single Image at 1 hour Suffice?</td>
</tr>
<tr>
<td>Merriam</td>
<td>Peer Review of Videood Teaching Encounters: A Novel Method for Continuing Teaching Education</td>
</tr>
<tr>
<td>Mutchler</td>
<td>Endothelial ENaC Modulates Vascular Reactivity</td>
</tr>
<tr>
<td>Najjar</td>
<td>Dose-seeking and efficacy study of pembrolizumab plus vemurafenib for therapy of advanced melanoma</td>
</tr>
<tr>
<td>Name</td>
<td>First Name</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>O'Brien</td>
<td>M. Emmet</td>
</tr>
<tr>
<td>Padgett</td>
<td>Shaylar</td>
</tr>
<tr>
<td>Prokopienko</td>
<td>Alexander</td>
</tr>
<tr>
<td>Qing</td>
<td>Hua</td>
</tr>
<tr>
<td>Rao</td>
<td>Mana</td>
</tr>
<tr>
<td>Rao</td>
<td>Mana</td>
</tr>
<tr>
<td>Samanta</td>
<td>Palash</td>
</tr>
<tr>
<td>Selk</td>
<td>Karen</td>
</tr>
<tr>
<td>Shah</td>
<td>Shivang</td>
</tr>
<tr>
<td>Shamir</td>
<td>Amith</td>
</tr>
<tr>
<td>Shelton</td>
<td>Celeste</td>
</tr>
<tr>
<td>Shipman</td>
<td>Katherine</td>
</tr>
<tr>
<td>Shively</td>
<td>Nathan</td>
</tr>
<tr>
<td>Shroff</td>
<td>Swati</td>
</tr>
<tr>
<td>Singh Paul</td>
<td>Rohan</td>
</tr>
<tr>
<td>Poster Author Index</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Suber</strong> Tomeka 21-B</td>
<td>FBXO17 Regulates GSK3β Polyubiquitination and Proteasomal Degradation in Lung Epithelial Cells</td>
</tr>
<tr>
<td><strong>Szymusiak</strong> John 73-B</td>
<td>An Innovative Patient Safety Curriculum For Pediatric Residents</td>
</tr>
<tr>
<td><strong>Szymusiak</strong> John 74-B</td>
<td>Internal Medicine Residents' Perceptions of Error Reporting: A Qualitative Study</td>
</tr>
<tr>
<td><strong>Thangudu</strong> Arti 64-B</td>
<td>Does DSME Position Statement Algorithm Improve Referrals?</td>
</tr>
<tr>
<td><strong>Tilstra</strong> Jeremy 22-B</td>
<td>B cell specific TLR9 is Protective in Murine Models of Systemic Autoimmunity</td>
</tr>
<tr>
<td><strong>Tilstra</strong> Jeremy 23-B</td>
<td>T cell exhaustion in Lupus Nephritis: A key to Understanding Autoimmunity and the Adverse Effects of Checkpoint Blockade</td>
</tr>
<tr>
<td><strong>Vanderberg</strong> Rachel 75-B</td>
<td>Back to the Bedside in the Outpatient Setting: Exam Room Presentations in Resident Continuity Clinic</td>
</tr>
<tr>
<td><strong>Vats</strong> Ravi 24-B</td>
<td>Neutrophils Occlude Precapillary Arterioles To Promote Neutrophil Extracellular Traps Dependent Lung Injury In Sickle Cell Disease</td>
</tr>
<tr>
<td><strong>Ward</strong> Keisha 65-B</td>
<td>Revisiting Antibiotic Stewardship in Long term Care Residents</td>
</tr>
<tr>
<td><strong>Winters</strong> Spencer 93-B</td>
<td>Idiopathic Pulmonary Fibrosis is Associated with Cytomeglovirus Relapse after Lung Transplantation – Are These Patients at Risk for other Herpesvirus Disease, Post-Transplant Lymphoproliferative Disease, or Malignancy?</td>
</tr>
<tr>
<td><strong>Winters</strong> Spencer 94-B</td>
<td>Short Telomere Length Predicts Poor Cytomegalovirus Outcomes in Lung Transplant Recipients with Idiopathic Pulmonary Fibrosis</td>
</tr>
<tr>
<td><strong>Yochum</strong> Zachary 25-B</td>
<td>EMT transcription factor TWIST1 mediates resistance to EGFR inhibitors in EGFR-mutant non-small cell lung cancer</td>
</tr>
<tr>
<td><strong>Zank</strong> Daniel 26-B</td>
<td>PTEN-induced putative kinase 1 modulates opening of the mitochondrial permeability transition pore through phosphorylation of adenine nucleotide translocase 2 and 3</td>
</tr>
</tbody>
</table>
1-B Poster: IL-17 signaling inducibly degrades ABIN1, a constitutive inhibitor of inflammatory signaling

Presenter: J. Cruz Agustin, Graduate Student
Research Interest: Bench Rheumatology and Clinical Immunology

Mentors: Sarah Gaffen PhD
Funding Source: NIH R01DE022550-01 R01-A1107825 (Gaffen)

Authors: J. Agustin Cruz BSc, Erin Childs MSc, Nilesh Amatya BS, Michelle Simpson-Abelson PhD, Abhishek Garg PhD, Rudi Beyaert PhD, Larry Kane PhD, Brian Aneskievich PhD, Averil Ma PhD, Sarah Gaffen PhD

Introduction: IL-17 is a pro-inflammatory cytokine that drives autoimmune diseases and promotes immunity to fungi. IL-17 binding to the IL-17 receptor initiates recruitment of adaptor proteins that activate NF-κB. IL-17 also induces expression of A20, a feedback inhibitor that restricts NF-κB activation and limits IL-17-dependent inflammation. ABIN1 is an A20 binding protein that has been implicated in autoimmune in human genetic studies, so we hypothesized that ABIN1 might also play a role in restricting IL-17-dependent signaling.

Methods: The promoter for the human ABIN1 (TNIP1) gene was cloned in the pGL4 luciferase system. We also used siRNA knock-down approaches, RT-PCR and western blotting.

Results: Indeed, ABIN1 inhibited the IL-17 pathway based on RNA silencing analyses. Specifically, the expression of the IL-17-dependent gene lipocalin 2 (Lcn2) increased at both basal levels and after stimulation upon ABIN1 knockdown. Consistently, reconstitution of ABIN1-deficient fibroblasts with ABIN1 also decreased both Lcn2 expression and promoter activation. However, while ABIN1 mRNA increased after IL-17A stimulation, ABIN1 protein progressively decreased following its inducible phosphorylation. Although feedback loops are commonly seen in signaling pathways, differential regulation of mRNA and protein of the same gene are not as common. Thus, we now propose that ABIN1 serves as a constitutive inhibitor of NF-κB signaling. While ABIN1 mRNA is induced by NF-κB at the mRNA level, removal of the ABIN1 protein is required to initiate signal transduction. Unexpectedly, we discovered that A20 is dispensable for both IL-17-mediated degradation of ABIN1 and for ABIN1-dependent inhibition of IL-17 signaling.

Conclusion: Altogether, these findings suggest that ABIN1 is a tonic NF-kB inhibitor, and that IL-17 signaling induces its degradation independently of A20 to enhance expression of NF-kB-dependent genes such as Lcn2.
2- B Poster: Post-transcriptional regulation of IL-17-dependent signal transduction

Presenter: Nilesh Amatya, Graduate Student
Research Interest: Bench Rheumatology and Clinical Immunology

Mentors: Sarah Gaffen PhD
Funding Source: None

Authors: Nilesh Amatya BS, Abhishek Garg PhD, Lawrence Kane PhD, Jay Kolls MD, Ulus Atasoy MD, Sarah Gaffen PhD

Introduction: Interleukin-17A (IL-17) is a proinflammatory cytokine essential in host defense against extracellular pathogens but also promotes inflammation in many autoimmune disease settings. IL-17 induces inflammatory signaling through de novo transcription and post-transcriptional regulation of downstream genes. One major mechanism of IL-17-mediated post-transcriptional gene regulation occurs through alterations in mRNA stability of target gene transcripts. Here, we report a new mechanism by which IL-17 increases the mRNA half-life of downstream target genes through the RNA binding protein known as Arid5a (AT-rich interactive domain-containing protein 5A). Arid5a was previously shown to stabilize Il6 (Interleukin-6) and Stat3 (Signal transducer and activator of transcription 3) transcripts by direct binding to the 3'UTR, thus counteracting the destabilizing effect of the endoribonuclease MCPIP1 (also known as Regnase-1).

Methods: To assess the role of Arid5a in IL-17 signaling, we performed gene knockdown using siRNA in the murine stromal cell line ST2. Following IL-17 treatment, expression of IL-17 target genes was analyzed using qRT-PCR and RNA-seq. mRNA half-life of IL-17 target genes was assessed after actinomycin D treatment. Arid5a-binding transcripts were identified via RNA immunoprecipitation. Co-immunoprecipitation assay was performed to study adaptor proteins that associate with Arid5a.

Results: siRNA knockdown of Arid5a resulted in reduced IL-17-dependent expression of Il6, Lcn2 (Lipocalin 2), Nfkbiz (which encodes I?B?), Cxcl1 and Cxcl5, but not Csf2 (GM-CSF). Arid5a significantly extended the half-life of Il6 mRNA in response to IL-17. Data from RNA immunoprecipitation assays demonstrated that Arid5a binds directly to Il6, Nfkbiz, Cxcl1, Cxcl5 but not Csf2 transcripts in an IL-17-dependent manner. In addition, Arid5a co-immunoprecipitated with TRAF2 and TRAF5, adaptors that have been implicated in IL-17-mediated mRNA stability. Moreover, Arid5a counteracted the destabilizing effect of MCPIP1 on IL-17 signaling. RNA-seq analysis following knockdown of Arid5a identified a specific subset of genes co-regulated by IL-17 and Arid5a, lending insight into the spectrum of gene targets regulated by this RNA binding protein.

Conclusion: In summary, Arid5a promotes the expression of a specific subset of IL-17 target mRNA transcripts in a TRAF2/5-induced pathway. Understanding the mechanisms underlying Arid5a specificity may help design novel therapeutic agents for IL-17 related autoimmune diseases.
**Introduction:** Relaxin-insulin like family peptide receptor 1 (RXFP1) codes the receptor for the peptide hormone, relaxin, which has been considered as a potential anti-fibrotic therapy for patients with tissue fibrosis. We have found decreased levels of RXFP1 expression in both the lung and lung fibroblasts from patients with Idiopathic Pulmonary Fibrosis (IPF). The lower expression levels of RXFP1 may represent a potential limitation for relaxin-based therapies in IPF patients. Reduced expression of RXFP1 was at the level of both mRNA and protein. We therefore hypothesized that aberrant transcriptional regulation may lead to RXFP1 down-regulation in IPF. Understanding the transcriptional regulation of RXFP1 may provide therapeutic opportunity to restore RXFP1 expression in IPF.

**Methods:** We determined the genomic structure of the regulatory region for the RXFP1 gene using bioinformatic analysis and publically available database. The putative promoter and enhancer regions were identified and cloned into luciferase reporter plasmids. The cloned DNA fragments were verified using DNA sequencing. Promoter activity of these reporter constructs were analyzed in HEK-293T cells using a dual luciferase assay.

**Results:** Multiple alternative transcripts have previously been identified for the RXFP1 gene in both UCSD Genome Browser and Ensemble. We identified two putative promoters separated by 204.4 kb DNA sequences in the RXFP1 gene locus. The proximal promoter was associated with most of the known RXFP1 transcripts while the distal promoter was associated with a longer transcript containing an additional 4 non-coding upstream exons. The distal promoter was predicted to be stronger (96%) than the proximal promoter (92%) based on promoter prediction (Berkeley Drosophila Genome Project (BDGP)) and promoter consensus matching. Multiple regions contain putative regulatory elements. We have cloned the putative distal (3.1kb) and proximal (1.4 kb) promoters into luciferase reporter vectors. Promoter activity was detected for both promoters in HEK-293T cells transiently expressing the RXFP1 luciferase promoter clones.

**Conclusion:** Two putative promoters separated by 204.4 kb DNA sequences were identified and functional in HEK-293T cells for the RXFP1 gene. Further characterization of these promoters and other regulatory regions in both normal and IPF lung fibroblasts will provide insight into the reduced expression of RXFP1 in IPF patients and may lead to new therapeutic targets for IPF.
**Poster Abstracts**

**5-B Poster:** Frataxin deficiency induces vascular metabolic dysregulation to promote pulmonary hypertension

**Presenter:** Miranda Culley, Graduate Student  
Vascular Medicine Institute

**Research Interest:** Bench

**Mentors:** Stephen Chan MD, PhD  
Funding Source: None

**Authors:** Miranda Culley BS, Jingsi Zhao MS, Ying Tang MS, Vinny Negi PhD, Stephen Chan MD, PhD

**Introduction:** Pulmonary hypertension (PH) is a vascular disease that results in increased pulmonary arterial pressure, right heart failure, and death. Our laboratory has demonstrated iron-sulfur (Fe-S) cluster deficiency promotes mitochondrial dysfunction and PH development. Frataxin (FXN) is a protein crucial to Fe-S cluster assembly. Genetic FXN deficiency causes Friedreich’s ataxia, a disease resulting in neurologic and cardiovascular dysfunction. The latter is often accompanied by PH, but the molecular etiology is unclear. Thus, there may be a direct role for FXN deficiency in PH development. We hypothesize FXN deficiency, due to genetic or acquired triggers, disrupts vascular cell metabolism to promote PH.

**Methods:** Manipulation of FXN expression was performed via lentivirus transduction and siRNA transfection in human pulmonary arterial endothelial and smooth muscle cells (HPAECs and HPASMCs) exposed to hypoxia and inflammation (IL-1). We measured FXN expression in response to mimic and anti-microRNA oligonucleotides and pharmacologic inhibition of bromodomain activity by I-BET151. Fe-S clusters were quantified with a fluorescent sensor; cell-specific changes, including apoptosis, migration, vasomotor gene expression, and hypertrophy, were measured. Mice were treated with endothelial-specific nanoparticles containing si-FXN followed by hypoxia.

**Results:** Both hypoxia and IL-1 down-regulated FXN expression in HPAECs while only hypoxia down-regulated FXN in HPASMCs. Hypoxia-induced miR-145 partially mediated FXN knockdown. I-BET151 partially restored FXN expression after hypoxic exposure and fully restored FXN after IL-1 exposure. We also found FXN deficiency decreased Fe-S cluster formation, leading to increased apoptosis and altered effectors of vasomotor tone in HPAECs and increased hypertrophy in HPASMCs. FXN knockdown under hypoxia increased right ventricular systolic pressures in vivo.

**Conclusion:** FXN expression is differentially regulated depending upon stressor and cell type. Furthermore, FXN deficiency promotes cell-specific vascular metabolic alterations that contribute to PH development in vivo. Taken together, we define a pathogenic mechanism centered on FXN’s role in Fe-S biogenesis, providing insight into the metabolic dysfunction that defines PH.
**6-B Poster:** Effect of Stretch on Umbrella Cell Tight Junctions

**Presenter:** Amity Eaton, Graduate Student
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** Gerard Apodaca PhD

**Funding Source:** R01 (Apodaca and Carattino)

**Authors:** Amity Eaton BS, Dennis Clayton BS, Luciana Gallo PhD, Nicolas Montalbetti PhD, Wily Ruiz BS, Marcelo Carattino PhD, Gerard Apodaca PhD

**Introduction:** Tight junctions (TJs) are composed of interconnected strands encircling epithelial cells at their apical borders, regulating paracellular permeability. Claudins are the main structural components of TJs. Claudins can be anionic, or cationic pore-formers, or can occlude the paracellular pathway, thereby altering epithelial permeability. Claudins expressed in different epithelia confer a unique ionic conductance, charge and size selectivity, and solute permeability to the paracellular pathway. Critically, TJs must maintain their function in the face of mechanical forces, such as urine accumulating in the bladder. Umbrella cells (UCs) form the outermost layer of the bladder epithelium. The UC apical membrane forms an exceptionally high resistance barrier, with relatively impermeable TJs, which must maintain their structure and function during cycles of bladder filling and voiding.

**Methods:** In situ bladder filling assay, immunofluorescence, adenoviral transduction.

**Results:** The TJ ring circumscribing each UC doubles in length when the bladder is filled, and recovers after 5 minutes of voiding. Unexpectedly, we observe an increase in junctional permeability with bladder filling, which recovers upon voiding. I have shown that bladder filling and voiding affect TJ claudin expression in rat bladder UCs, in-vivo. Specifically, pore-forming claudins increase in expression with bladder filling, which could explain the increase in permeability with bladder filling. These data indicate that the urothelial TJ undergoes stretch-induced remodeling. In addition to these observations, we have previously published that the apical membrane of UCs expands upon filling via Rab-dependent exocytosis; and is internalized via compensatory endocytosis, upon voiding. Based on these observations, it is plausible that the TJ ring expands and pore-forming claudins are delivered via exocytosis when the urothelium is stretched, and the TJ ring contracts and pore-forming claudins are internalized via endocytosis upon voiding. This hypothesis is supported by my observations that inhibition of exocytosis prevents TJ ring expansion when the bladder is filled; and conversely, inhibition of endocytosis prevents TJ ring contraction and claudin redistribution with bladder voiding. These data indicate a role for exocytosis and endocytosis in TJ remodeling throughout the bladder cycle. Interestingly, Rab13 promotes assembly of the TJ via exocytosis of claudins, localizes near TJ in UC, and we have shown that expression of dominant-negative Rab13 (DN-Rab13) prevents stretch-induced TJ ring expansion.

**Conclusion:** These data support a role for Rab13-dependent exocytosis of pore-forming claudins mediating TJ ring expansion and the increase in paracellular permeability with bladder filling, and endocytosis of pore-forming claudins mediating TJ ring contraction and recovery of paracellular resistance upon voiding.
Introduction: Proximal tubule (PT) dysfunction, including tubular proteinuria, is a significant complication in sickle cell disease (SCD) that can eventually lead to chronic kidney disease. The PT is especially susceptible to cytotoxic damage, and tubular dysfunction in SCD is thought to result from prolonged exposure to hemoglobin released from damaged red blood cells. Filtered hemoglobin dimers are internalized into PT cells upon binding to the multiligand receptors megalin and cubilin. These receptors bind to numerous other filtered proteins, including albumin and vitamin D binding protein, and are important for maintaining vitamin D homeostasis and protein-free urine. We hypothesized that exposure of PT cells to hemoglobin would impair endocytic uptake of megalin/cubilin ligands to cause tubular proteinuria.

Methods: We used spectrofluorimetric and imaging approaches to quantify the effects of hemoglobin on endocytic uptake of fluorescent albumin and vitamin D binding protein in a PT cell line. Expression of heme oxygenase 1 (HO-1) was quantified by western blotting.

Results: We found that concentrations of hemoglobin predicted to enter the tubule lumen during hemolytic crisis profoundly inhibit the uptake of other megalin/cubilin ligands (albumin and vitamin D binding protein) by PT cells. These effects were independent of heme reduction state, occurred in the absence of a cytotoxic response, and appear to be due to direct competition for megalin/cubilin binding. The Glu7Val mutant of hemoglobin that causes SCD was equally effective at inhibiting albumin uptake compared with WT hemoglobin. Haptoglobin restored albumin uptake in the presence of hemoglobin, suggesting that haptoglobin binding to the hemoglobin αβ dimer-dimer interface interferes with hemoglobin binding to megalin/cubilin. BLAST searches and structural modeling analyses revealed regions of similarity between hemoglobin and albumin that map to this region and may represent sites of hemoglobin interaction with megalin/cubilin. Using these data, we established a 96-well assay that enables us to screen for selective inhibitors of hemoglobin uptake that preserve PT function.

Conclusion: Our studies suggest that the primary cause of tubular proteinuria in SCD is impaired endocytosis of megalin/cubilin ligands due to competition from filtered hemoglobin. Our results have therapeutic implications for SCD, as preventing hemoglobin uptake is predicted to slow the progression of kidney disease. Additionally, our data suggest a potential explanation for the vitamin D deficiency commonly observed in sickle cell patients. Ongoing studies include quantitation of vitamin D metabolites in patient serum to assess whether they correlate with hemolysis, and experiments to refine our screen for inhibitors of hemoglobin uptake.
**8-B Poster:** CpG DNA Promotes Lysosomal Degradation of the Receptor for Advanced Glycation End Products (RAGE) through F Box Protein FBXO10-mediated Ubiquitination

**Presenter:** John Evankovich, Fellow

**Research Interest:** Bench Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Rama Mallampalli MD, Bill Chen PhD

**Funding Source:** T32

**Authors:** John Evankovich MD, Alison Mckelvey BS, Sarah Dunn BS, Traivs Lear BS, Bill Chen PhD, Rama Mallampalli MD

**Introduction:** CpG DNA are Damage Associated Molecular Pattern (DAMP) molecules originating from bacteria or host mitochondria which are elevated in patients with critical illness and acute respiratory distress syndrome (ARDS). The receptor for advanced glycation end products (RAGE) is a membrane receptor highly enriched in pulmonary epithelial cells that binds CpG DNA at the cell surface and delivers it to intracellular endosomes, driving excessive inflammation and cellular injury. The upstream signaling events that initiate CpG DNA/RAGE-mediated epithelial cell injury are unknown. We have previously shown that RAGE is a substrate for the orphan F Box Protein (FBXO10), which targets RAGE for ubiquitination and lysosomal degradation. We hypothesized that pathogenic CpG DNA would increase RAGE ubiquitination and lysosomal degradation through FBXO10, contributing to excessive epithelial cellular injury.

**Methods:** The human bronchial epithelial Cell line, Beas2B was used for all experiments. Cells were stimulated with ODN2006, a CpG DNA oligonucleotide known to bind RAGE. Immunoblots for RAGE and FBXO10 were performed after CpG DNA stimulation. Cells were transiently transfected with epitope tagged RAGE (V5HisRAGE) for subsequent immunoblotting, His purification, and coimmunoprecipitation (CoIP) experiments to determine the effect of ODN2006 on RAGE phosphorylation, FBXO10 interaction, and ubiquitination. FBXO10 siRNA was used to decrease FBXO10 levels.

**Results:** RAGE levels decrease significantly after 15 minutes of CpG DNA treatment. RAGE levels also decreased in a CpG DNA dosedependent manner at 1h. Mechanistically, CpG DNA increased RAGE phosphorylation at Serine 391, a site have previously shown critical for FBXO10 recruitment. CpG DNA enhanced RAGE/FBXO10 interaction and increased ubiquitinated RAGE, directing it for lysosomal degradation. CpG DNA-mediated RAGE degradation was prevented with either pretreatment with the lysosomal hydrolase inhibitor Leupeptin or knockdown of FBXO10 with siRNA.

**Conclusion:** We provide a novel mechanism by which a pathogenic ligand elevated in ARDS, CpG DNA, reduces RAGE levels in pulmonary epithelial cells. CpG DNA promotes RAGE phosphorylation, enhancing recruitment of the E3Ligase subunit FBXO10, which ubiquitinates RAGE and directs it for lysosomal degradation. FBXO10 inhibition may be a novel target to prevent RAGE degradation, rendering epithelial cells more resistant to injury in the presence of CpG DNA.
**Introduction:** The NNRTIs dapivirine (DAP), rilpivirine (RPV) and the phenylethylthiazolylthiourea analog MIV-150 are in development as pre-exposure prophylaxis (PrEP) modalities to prevent the acquisition of HIV-1 infection. Currently, there is a paucity of information in regard to the resistance and cross-resistance profiles of DAP and MIV-150, which we addressed in this study.

**Methods:** Twenty-eight subtype B HIV-1LAI infectious viruses containing single NNRTI resistance mutations spanning 17 different codons (V90I; L100I/V; K101E/P; K103N/S; V106I; V108I; E138A/K; V179D/F; G190A/S; I181C/I/V; Y188C/H/L; H221Y; P225H; F227C/L; M230L; P236L; N348I) were constructed by site-directed mutagenesis. Drug susceptibility in a single cycle assay using TZM-bl cells was determined for RPV, DAP and MIV-150. Low-, intermediate- and high-level resistance was defined as 2–8, 8–20, and >20-fold changes in drug susceptibility compared to the wild type virus.

**Results:** Of the 3 NNRTIs studied, RPV exhibited the best antiviral activity across the panel of HIV-1 variants tested. RPV was found to be active against 19 of 28 variants, with low-level resistance conferred by the E138A/K, F227C, K101E, Y188L and M230L mutant viruses, and high-level resistance conferred by Y181I/V and K101P. DAP was active against only 15 of the 28 viruses. The K101E, E138K, K103N/S, F227C, Y181C and L100V viruses conferred low resistance to RPV; whereas the L100I and M230L and Y188L, K101P and Y181I/V viruses were found to confer intermediate and high-level resistance, respectively. MIV-150 was also active against only 15 of the HIV-1 variants tested: K101E and L100I/V; F227C and Y181C; and M230L, K103N/S, Y181I/V, Y188L and K101P mutations conferred low-, intermediate and high-level resistance, respectively.

**Conclusion:** DAP and MIV-150 activity is compromised by many HIV-1 variants containing a single NNRTI resistance mutation. Both NNRTIs exhibit decreased susceptibility toward the K101E, K103N and Y181C mutations which are major NNRTI transmitted drug resistance mutations in all geographic regions and HIV-1 subtypes.
**Introduction:** Th17 cells are implicated in autoimmunity, including attack of the central nervous system (CNS) in multiple sclerosis. β-site APP-cleaving enzyme 1 (BACE1) is a membrane protease expressed in neurons and astrocytes, with a known role in Alzheimer's disease (AD). BACE1 also contributes to lesion severity following brain injury, as does IL-17, although these two molecules have not previously been linked. In this study, we aim to elucidate the role of BACE1 in Th17 function in vitro and during autoimmune CNS inflammation.

**Methods:** In vitro differentiation studies were used to evaluate transcriptional and functional differences in Th development. The role of BACE1 was tested in Experimental Autoimmune Encephalomyelitis (EAE), the mouse model of Multiple Sclerosis (MS). Passive transfer of autoreactive Th17 cells as well as adoptive transfer of T cells into RAG-/- mice followed by immunization with an immunogenic myelin antigen allowed us to address the importance of BACE1 deficiency in a T cell-specific manner.

**Results:** In vitro-differentiated BACE1-/- Th17 cells exhibited reduced IL-17A production despite regular RORgt upregulation. Expression of IL-17F was mildly reduced while other prototypic Th17 molecules were unaltered. Interestingly, other T helper subsets remained unaffected. Conversely, overexpression of BACE1 increased IL-17A levels. In vivo, BACE1-/- autoreactive T cells were similarly defective in IL-17A expression. Transfer experiments demonstrated that BACE1-/- T cells present blunted pathogenic function, conferring resistance to EAE. Mechanistically, BACE-/- T cells exhibited sustained Akt phosphorylation, suggesting a perturbation of the PTEN-Akt axis.

**Conclusion:** We here report a novel role for the brain-associated enzyme BACE1 in Th17 function, its expression being crucial for induction of EAE. BACE1 regulates IL-17A expression in RORgt+ Th17 cells, through a cell-intrinsic mechanism involving Akt signaling. Taken together, our data project a potential for BACE1 inhibition for the treatment of autoimmunity.
11-B Poster: ATPIF1 knockout (KO) mice are protected from diet-induced obesity (DIO) and glucose intolerance.

Presenter: Brydie Huckestein, Graduate Student  
Research Interest: Bench Endocrinology and Metabolism

Mentors: Michael Jurczak PhD  
Funding Source: Internal Funds

Authors: Brydie Huckestein BS, Lia Edmunds PhD, Yingze Zhang PhD, Yanxia Chu MD, Michael Jurczak PhD

Introduction: The etiology of obesity is complex and likely influenced by factors other than overfeeding and reduced activity. Differences in energy efficiency may be one such factor and could provide a novel mechanism for treating obesity. ATPase inhibitory factor 1 (ATPIF1) inhibits the ATPase activity of ATP synthase such that inhibition of ATPIF1 may reduce mitochondrial efficiency by promoting ATP consumption and proton transport against a concentration gradient by ATP synthase.

Methods: To determine how ATPIF1 loss impacts energy balance in vivo, we studied WT and ATPIF1 KO mice fed regular chow (RC) or high-fat diet (HFD; 60% kcal fat) for ~10 weeks. To track differences in adiposity, we performed EchoMRI on mice at the end of dietary challenge. We performed glucose tolerance tests (GTT) on mice to look for differences in blood glucose values and insulin sensitivity and utilized the CLAMS system to detect potential differences in feeding and activity.

Results: There were no differences in body weight (BW), fat or lean mass between RC groups. In contrast, HFD caused a significant (P<0.001) 40% increase in BW in WT, but only a 20% non-significant increase in KO mice. HFD WT weighed 25% more than KO mice (P<0.01), which was accounted for by increased adiposity (P<0.01) and no change in lean mass. Preliminary metabolic cage studies (n=4/group) detected no significant differences in energy expenditure, activity or feeding that accounted for protection from DIO. Plasma leptin was 50% less in HFD KO compared with WT mice and plasma resistin was similarly 45% less. Six-hour fasted plasma glucose and insulin did not differ between HFD groups, but KO mice displayed significantly reduced plasma glucose during GTT (P<0.05 t=30-120 min) and glucose AUC was 15% less (P<0.05). Insulin levels during GTT were qualitatively different between groups. Glucose dosing had no effect on insulin in WT, but caused a two-fold increase in insulin in KO mice from zero to 15 min that returned to 40% of baseline by 120 min. Ectopic lipid is associated with insulin resistance, but there were no differences in triglyceride content in skeletal muscle from HFD WT and KO mice.

Conclusion: Future studies to determine how ATIPF1 deletion affects mitochondrial bioenergetics and the mechanism(s) for protection from DIO and improved GTT are of great interest.
**12-B Poster:** Mechanism of endothelial cell calcium influx during sonoreperfusion therapy

**Presenter:** Filip Istvanic, Graduate Student  
**Cardiology**

**Research Interest:** Bench Cardiology

**Mentors:** John Pacella MD

**Funding Source:** Pitt Med Physician Scientist Training Program

**Authors:** Filip Istvanic BS, Francois Yu PhD, Xucai Chen PhD, John Pacella MD

**Introduction:** Microembolization during percutaneous coronary intervention for acute myocardial infarction causes microvascular obstruction (MVO). We have demonstrated that sonoreperfusion (SRP) therapy using ultrasound (US) and microbubbles (MBs) relieves MVO in vitro and in vivo. We have shown that inhibition of the endothelial nitric oxide (NO) pathway attenuates SRP in vivo. Endothelial cell calcium influx triggers the release of NO, which ameliorates many of the sequelae of MVO. In this study, we explored the previously unknown mechanism by which SRP upregulates endothelial calcium entry. Sonoporation, or the formation of transient pores in cell membranes following US and MB therapy, results in endothelial cell calcium influx. Additionally, transient receptor potential cation channel subfamily V member 4 (TRPV4), a shear-stress mediated calcium channel mechanosensor, has also been implicated in endothelial NO upregulation. We hypothesized that both sonoporation and the TRPV4 pathway contribute to endothelial cell calcium entry during SRP.

**Methods:** Lipid MBs and US were applied to cultured human umbilical vein endothelial cells (HUVECs). One group of cells received the TRPV4 inhibitor, HC-067047. Propidium iodide (PI) and fluo-4 AM were used during each experiment to detect sonoporation and to visualize calcium influx, respectively. Cells were imaged fluorescently before, during, and after US treatment.

**Results:** HUVECs were exposed to a wide spectrum of US conditions with and without TRPV4 inhibition. Our analysis revealed that TRPV4 inhibition had no predictable effect on calcium influx relative to control (p=0.19). Despite large variabilities in our preliminary data, it was striking to observe that 98.5±1.9% of cells that increased in calcium intensity with TRPV4 inhibitor did not display PI, suggesting that calcium influx in this particular subset of cells occurred independently of both TRPV4 and sonoporation.

**Conclusion:** In HUVECs with TRPV4 inhibitor, calcium entry occurred independently of both TRPV4 and sonoporation suggesting that other shear-stress mechanosensors may contribute to calcium entry. Further studies are needed to determine the relative contribution of TRPV4 to SRP. Future directions include analyzing the potential contribution of G-protein coupled receptors to calcium entry during SRP and identifying US conditions that predict sonoporation-independent calcium entry.
**13-B Poster:** OVLT Neuron Responses to Hypertonic NaCl and Mannitol Differ: Implications for Neural Regulation of Blood Pressure by NaCl

**Presenter:** Brian Kinsman, Graduate Student  
**Research Interest:** Bench Renal-Electrolyte

**Mentors:** Sean Stocker PhD  
**Funding Source:** NRSA 1F30HL131269-01A1

**Authors:** Brian Kinsman BA, Kirsteen Browning PhD, Sean Stocker PhD

**Introduction:** Central infusion of hypertonic NaCl raises sympathetic nerve activity (SNA) and arterial blood pressure (ABP). These sympathoexcitatory pressor responses are largely attenuated by lesion or pharmacologic inhibition of sites along the lamina terminalis, namely the organum vasculosum of the lamina terminalis (OVLT). Canonically, OVLT seats brain osmoreceptors. However, central infusion of hypertonic osmolytes (eg. mannitol, sorbitol) does not raise ABP as greatly as central infusion of NaCl. Whether separate osmoreceptor versus sodium receptor mechanisms within OVLT distinguish these responses remains unknown. Therefore, we hypothesized that hypertonic NaCl and mannitol/sorbitol excite OVLT neurons by different mechanisms to regulate SNA and ABP.

**Methods:** To assess this hypothesis, in vitro whole-cell patch clamp recordings were performed on OVLT neurons in acutely isolated adult Sprague-Dawley rat brain slices. In current clamp, action potential (AP) frequency was measure at baseline (3-5min), during sequence-randomized bath application of equi-hyperosmotic NaCl (+7.5mM) or mannitol (+15mM) krebs buffers (3min), stimulus washout (5-10min), and sequence repetition with the alternate osmotic stimulus. In a parallel set of in vivo experiments, lumbar SNA, adrenal SNA and ABP were measured in anesthetized adult rats (n=3-4) in response to equi-hyperosmotic intracerebroventricular (ICV) infusions (5µL/10min) of NaCl (1.0M) and sorbitol (2.0M).

**Results:** Among the majority of OVLT neurons in vitro (total n=36 neurons from 32 rats), AP frequency increased >25% from baseline in response to both (18/36) hypertonic NaCl (1.26±0.25 Hz to 2.16±0.36 Hz, p<0.05 compared to baseline) and mannitol (1.13±0.25 Hz to 1.58±0.28 Hz, p<0.05). Interestingly, osmotically equivalent hypertonic NaCl and mannitol stimuli (+15mOsm) elicited quantitatively different responses in the same OVLT neuron. The increase in AP frequency was significantly greater in response to NaCl (?AP frequency from baseline = 0.90±0.21 Hz) than mannitol (?AP frequency from baseline = 0.45±0.07 Hz, p<0.05). Smaller proportions of OVLT neurons were either excited by NaCl alone (8/36), mannitol alone (3/36), or non-responsive to both stimuli (7/36). Furthermore, in vivo ICV infusion of NaCl versus sorbitol produced significantly greater increases in lumbar SNA (NaCl: +23±2%, sorbitol: +9±1%, p<0.05), adrenal SNA (NaCl: +9±2%, sorbitol: +4±4%, p<0.05), and ABP (NaCl: +12±2mmHg, sorbitol: 1±1mmHg, p<0.05).

**Conclusion:** Collectively, these different OVLT response profiles to mannitol or sorbitol versus NaCl may represent distinct osmoreceptor versus sodium receptor mechanisms and contribute to the contrasting effects of ICV NaCl versus other osmolytes on SNA and ABP.
14-B Poster: Chemical Inhibition of DCUN1D1, a New Approach of Targeting Cullin Neddylation for Lung Cancer Treatment

Presenter: Travis Lear, Graduate Student
Research Interest: Bench Pulmonary, Allergy and Critical Care Medicine

Mentors: Bill Chen PhD
Funding Source: None

Authors: Travis Lear BA, Yuan Liu MD, Alison Mc Kelvey BS, Sarah Dunn BS, Bill Chen PhD

Introduction: Cullin based E3 ligases such as CRL1 have profound roles in regulating cell cycle progression, mitosis, and DNA repair; all linked to cancer initiation and progression[1]. The activity of the SCF complex is highly dependent on NEDD8 conjugation to the Cullin protein. So far, there is only one inhibitor, MLN4924, which targets the upstream pathway of Cullin Neddylation, thus disrupting SCF-E3 activity and leading to cell cycle arrest and tumor apoptosis. However, protein DCUN1D1 is also one of the essential components of NEDD8 conjugation pathway, [2] and has been implicated as a factor for squamous cell carcinoma development in the lung [3]. We hypothesized pharmacological inhibition of DCUN1D1 could blunt tumor progression.

Methods: DCUN1D1 protein was pharmacologically modeled and subjected to in silico compound screening and score-ranked binding simulations. Hit compound BC-1526 was chemically optimized to lead BC-1558, efficacy being measured through NEDD8-Cullin conjugation, CRL substrate level, cellular proliferative ability, and cell cycle inhibition. Nu/Nu athymic mice (n = 5-7) were implanted with human cancer cell xenografts subcutaneously prior to treatment with BC-1558.

Results: Here, we developed a new small molecule, BC-1558, which selectively disrupts DCUN1D1/UBC12 interaction, inhibits Cullin Neddylation in cells, induces human cancer cell apoptosis/cell cycle arrest, and blunts tumor progression in multiple tumor xenografts. We also showed excellent efficacy of BC-1558 in MLN4924 resistant cancer cells. Our data suggest that DCUN1D1 inhibitor may provide a new approach targeting the Neddylation cascade for cancer treatment.

**Poster Abstracts**

**15-B Poster:** Relaxin Reduces Inflammatory Gene Expression in Aged Rats

**Presenter:** Brian Martin, Graduate Student  
Vascular Medicine Institute  
**Research Interest:** Bench

**Mentors:** Guy Salama PhD  
**Funding Source:** None

**Authors:** Brian Martin BS, Beth Gabris BS, Guillermo Romero PhD, Ansuman Chattopadhyay PhD, Guy Salama PhD

**Introduction:** Aging is associated with a higher prevalence of heart failure (HF) likely due to maladaptive structural (fibrosis, hypertrophy) and electrical (decreased conduction velocity) cardiac remodeling. Evidence suggests there is a low-grade, chronic inflammation during aging and the term “inflammaging” has been used to describe the pervasiveness of inflammation in most age-related diseases. The classic pro-inflammatory cytokines implicated in HF include tumor necrosis factor a (TNFa), interleukin (IL)-1 and IL-6. Relaxin (RLX), a hormone discovered for its role during pregnancy, has been shown to reduce neutrophil activation, and decrease circulating levels of the classic cytokines in THP-1 cells. Significantly, RLX has shown improvements in 180-day cardiovascular and all-cause mortality in HF patients after 48-hours RLX treatment. However, given the short lifespan of RLX (~2hrs), the mechanisms underlying RLXs long term beneficial effects remain unclear. A plausible explanation for these long-term effects is a significant effect of RLX on gene expression.

**Methods:** Aged (24-month) and young (9-month) male F-344 rats were treated with vehicle or RLX (400 µg/kg/day) for 14 days followed by RNA-Sequencing and pathway analysis and Picro Sirius Red and Wheat Germ Agglutinin staining of the left ventricles (LV).

**Results:** RLX significantly reduced fibrosis (23%) and cellular hypertrophy (10%) in the LV and increased conduction velocity (20%). RLX significantly reduced transcript expression (fold change) of TNFa (-1.82), IL-1b (-3.34) and IL-6 (-4.35) and similarly, pathway analysis showed RLX inhibited signaling through IL-6, TNFR1, TNFR2 and HMGB1 pathways. In addition, RLX significantly activated the LXR/RXR and PPAR pathways, which have known anti-inflammatory effects. Pathway analysis also showed RLX significantly decreased recruitment of leukocytes, phagocytes and neutrophils, through a downregulation of multiple immune cell attractants or activators, including: CCL2 (-3.26), CCL3 (-2.62), CCL7 (-2.65), CXCL2 (-2.42), CXCL3 (-3.54), CXCL10 (-2.03) and FOS (-2.24). Finally, in aging, the NRF2 mediated oxidative stress response is significantly activated, and subsequently inhibited by RLX, suggesting a down-regulation of oxidative stress by RLX.

**Conclusion:** Taken together, these data suggest RLX acts via genomic mechanisms to significantly reduce pro-inflammatory transcripts in aged rats. Genomic modifications may help explain RLXs long-term beneficial effects seen in HF patients. More work is needed to determine RLXs effect on circulating levels of inflammatory cytokines and monocyte or leukocyte activation in myocytes and intact cardiac tissue.
**16-B Poster:** Endothelial ENaC Modulates Vascular Reactivity

**Presenter:** Stephanie Mutchler, Graduate Student  
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** Thomas Kleyman MD

**Funding Source:** T32

**Authors:** Stephanie Mutchler BS, Thomas Kleyman MD

**Introduction:** The epithelial sodium channel (ENaC) is well known for its role in regulating sodium absorption in the distal nephron. ENaC is also found in endothelial cells and smooth muscle of the vasculature. While little is known about the function of endothelial ENaC (EnENaC) in vivo, cell culture data suggests it regulates nitric oxide levels, as increased activity of the channel reportedly stiffens the cortical actin cytoskeleton, which decreases sensitivity to shear stress and reduces nitric oxide levels. These observations raise the possibility that EnENaC has a role in regulating vascular tone and blood pressure.

**Methods:** We utilized pressure myography to examine the effects of EnENaC on vasoreactivity of a small resistance-like (thoracodorsal) artery from mice maintained on a control diet (CD) or either a high salt diet (HSD) or a low salt diet (LSD) to induce extracellular volume expansion or depletion, respectively. A specific inhibitor of ENaC,amiloride, was added to the vessel lumen to assess the role of EnENaC in promoting or preventing vasodilation. ENaC expression was assessed in arteries by immunofluorescence microscopy.

**Results:** Vessels from animals on CD had no change in response to the vasodilator acetylcholine with amiloride. Vessels from animals on LSD for 1 week had normal response to acetylcholine. The acetylcholine response decreased in the presence of amiloride, suggesting that EnENaC is promoting vasodilation in these vessels. In vessels from animals on HSD, acetylcholine +/- amiloride responses were dependent upon length of time on the HSD. Vessels from mice on 2 weeks of HSD showed decreased acetylcholine response that was rescued by ENaC inhibition. In contrast, vessels from animals maintained on HSD for longer time points had a reversal in this response, with ENaC inhibition impairing the vasodilatory response. We are currently conducting studies utilizing L-NAME to determine whether any changes in the acetylcholine vasodilatory response are nitric oxide mediated.

**Conclusion:** Endothelial ENaC appears to modulate vascular reactivity in vivo. Whether it promotes or inhibits vasodilation is dependent upon volume status as well as the duration in the change of volume. Further studies are needed to determine whether ENaC affects nitric oxide levels, or whether the channel alters the acetylcholine vasodilatory response through other mechanisms. Future work will be performed in endothelial and vascular smooth muscle ENaC knockout mice to better discern the role of vascular ENaC in vivo.
**18-B Poster:** Telomerase Deficiency in Macrophages Decreases Atherosclerosis Formation by Silencing Inflammatory STAT3 Signaling

**Presenter:** Hua Qing, Graduate Student

**Research Interest:** Bench Vascular Medicine Institute

**Mentors:** Dennis Bruemmer MD

**Funding Source:** AHA

**Authors:** Hua Qing MD, Dennis Bruemmer MD

**Introduction:** Telomerase Reverse Transcriptase (TERT), the catalytic subunit of telomerase, supports critical cellular responses required for tissue remodeling. Previous studies established that TERT expression is induced in activated macrophages and during experimental and human atherosclerosis formation. In the present study, we investigated the role of TERT for atherosclerosis development and macrophage inflammation.

**Methods:** TERT-deficient mice were crossbred with LDL-receptor-deficient (LDLr-/−) mice to generate first generation G1TERT-/-/LDLr-/- offsprings, which were then further intercrossed with G1TERT-/-/LDLr-/- cousins to obtain late generation G3TERT-/-/LDLr-/- mice. Furthermore, chimeric LDLr-/- mice with macrophage-specific deletion of TERT was obtained by bone marrow transplantation. Atherosclerosis was quantified by en face analysis, as well as the immunostaining for macrophages and foam cells in the aortic roots.

**Results:** G1TERT-/-/LDLr-/- mice revealed no telomere shortening while obvious telomere attrition was evident in G3TERT-/-/LDLr-/- mice. When fed an atherogenic diet, G1TERT-/-/LDLr-/- and G3TERT-/-/LDLr-/- mice were both protected from atherosclerosis formation compared to their wildtype controls, indicating that genetic TERT-deletion prevents atherosclerosis, and formation of the disease is not affected by telomere attrition. Similarly, atherosclerosis development was decreased in chimeric LDLr-/- mice with TERT deletion in macrophages. TERT deficiency decreased macrophage accumulation in lesions and decreased chemokine expression. Sequence analysis of silenced inflammatory gene promoters indicated that TERT deletion alters STAT3 signaling, which was confirmed in atherosclerotic plaques from LDLr-/- mice with macrophage-specific deletion of TERT. In isolated macrophages, TERT was required for STAT3 signaling and its recruitment to target chromatin of STAT3-dependent promoters.

**Conclusion:** We propose that genetic TERT deficiency decreases atherosclerosis formation by silencing inflammatory chemokine transcription through decreased STAT3 recruitment to target promoters.
**Poster Abstracts**

**19-B Poster:** Candida albicans (CA) gene expression in vivo identifies copper homeostasis as an important biological process during intra-abdominal candidiasis (IAC)

**Presenter:** Palash Samanta, Fellow
Infectious Diseases

**Research Interest:** Bench

**Mentors:**
Hong Nguyen MD
Cornelius Clancy MD

**Funding Source:** NIH

**Authors:** Palash Samanta MD, Cornelius Clancy MD, Shaoji Cheng MD, Hong Nguyen MD

**Introduction:** IAC is common and carries a high mortality. IAC pathogenesis is poorly understood. We have developed a murine IAC model that mimics diseases observed in humans. Understanding pathogenesis of IAC is crucial for novel therapeutic development. Transcriptional profiling in vivo is a powerful tool for understanding processes and virulence factors important in pathogenesis

**Methods:** We performed RNA-Seq on peritoneal fluid (PF) and intraabdominal abscesses (IAA) recovered from mice after peritoneal inoculation of CA SC5314+ sterile stool (SS)

**Results:** IAC began as peritonitis. CA PF burdens decreased from 6 to 72h (p=0.0004), and cleared by 7d. PMN infiltrate was minimal at 6h, peaked at 24h, and switched to lymphocyte by 48h. IAA were evident at 48h, and persisted for 14d. CA total reads were =7 million. RNA-Seq identified 117 CA genes significantly upregulated in 24h PF vs 48h IAA, and 141 up in IAA vs PF. Upregulated PF and IAA genes were over-represented for oxidation-reduction and Cu homeostasis, respectively (p=0.0005, 0.0004). Since Cu is both an essential microbial nutrient and toxin, we measured [Cu] and expression of 32 CA Cu-associated genes in PF and overnight culture (OC) by qRT-PCR. Cu was undetectable in supernatant of overnight culture but median [Cu] continued to increase in PF as the infection progressed (p=0.03). SOD5 and COX17 were upregulated in PF at 30min post-infection (PI) compared to OC, probably represents response to stress in vivo. 25 genes (= 10-folds) including response to oxidative stress, increased [Cu] (Cu exporters and metallothioneins) and several transcription factors were upregulated in PF at 24h compared to PF at 30min. This response, along with PMN surge, is in concordance to heightened response to stress and steady increased [Cu]. At 48h, 21 genes were downregulated in PF compared to PF 24h, suggesting decreased stress, reflected by switching from PMN to lymphocyte. Interestingly, gene expression data is in discordance with high [Cu] at 48h, probably secondary to overall stabilization of micro-environment in response to stress or exhaustion of genetic machinery

**Conclusion:** Cu homeostasis is complex and dynamic during IAC. PF [Cu] increases during peritonitis, unlike during disseminated candidiasis. However, CA Cu transcriptional responses to Cu homeostasis at 24-48h are directed to overall increase in stress, and increase in [Cu] become dysregulated as peritonitis progresses, which may be adaptive to different in vivo niches, or maladaptive as CA is cleared by the host. We have knocked out three Cu transcription factor genes and are testing them in murine IAC model to evaluate their role in virulence
**20-B Poster:** Acute modulation of proximal tubule endocytic capacity by fluid shear-stress

**Presenter:** Katherine Shipman, Graduate Student  
Renal-Electrolyte

**Research Interest:** Bench

**Mentors:** Ora Weisz PhD  

**Funding Source:** R01

**Authors:** Katherine Shipman BS, Kimberly Long PhD, Youssef Rbaibi BS, Catherine Baty DVM, PhD, Ora Weisz PhD

**Introduction:** Epithelial cells composing the proximal tubule (PT) of the kidney are responsible for the reabsorption of low molecular weight (LMW) proteins and other small molecules from the glomerular ultrafiltrate. This reabsorption is necessary to recover essential nutrients and maintain protein-free urine. Tubular proteinuria is often an early sign of kidney damage and is observed in many clinical settings, including genetic disorders, early stages of diabetes, sickle cell disease, and post renal transplantation. A limitation in understanding the regulation of receptor-mediated apical endocytosis of filtered LMW proteins has been the lack of a highly differentiated cell culture model for the proximal tubule.

**Methods:** Because PT cells in vivo are continually exposed to flow, we have cultured cells under continuous fluid shear stress (FSS) to better recapitulate this environment. Opossum kidney cells were plated on permeable filter supports, and the following day were either exposed to orbital FSS or maintained under static conditions for an additional four days.

**Results:** Ultrastructural analysis revealed striking differentiation of the apical brush border and endocytic pathway in cells exposed to FSS, similar to that observed in PT cells in vivo. Culture under FSS also had dramatic effects on lysosomal and mitochondrial biogenesis, as well as expression of Na+/K+-ATPase and V-ATPase. Endocytic capacity per cell, quantified based on the uptake of fluorescently-labeled albumin, was increased by ~ five-fold in cells cultured under FSS. Endocytic uptake was rapidly and reversibly decreased when FSS was reduced. Consistent with enhanced endocytosis, we found a significant increase in expression and a change in distribution of Rab11a, a marker of recycling endosomes, in cells cultured under FSS.

**Conclusion:** We have developed a culture system that results in highly differentiated and polarized PT cells that modulate endocytic capacity in response to acute changes in FSS. We are currently working to identify changes in other trafficking proteins that will be used to construct a testable model for how the endocytic pathway is acutely regulated in differentiated PT cells.
**Introduction:** Glycogen synthase kinase-3β (GSK3β) is a highly conserved serine-threonine kinase that is a critical regulator of cell differentiation, metabolism, development, and inflammation. GSK3β-mediated phosphorylation is a key step in targeting substrates of Skp1/Cul1/F-box protein (SCF) E3 ubiquitin ligases to the proteasome for degradation. Recent data suggest that GSK3β has critical roles in propagating inflammation in murine models of acute lung injury. The goal of our study was to understand how GSK3β protein stability is regulated and how these mechanisms may influence inflammation in murine lung epithelial cells.

**Methods:** Site-directed mutagenesis was used to generate lysine to arginine point mutations in GSK3β. Plasmids expressing hemagglutinin (HA)-tagged wild-type, K183R, and K205R mutant GSK3β were transfected into murine lung epithelial cells (MLE-12). After cells were cultured for 48 h, a cycloheximide chase assay (40 g/mL) was performed to evaluate the half-life of GSK3β. Lysates were collected at 0, 2, 4, and 8 h and immunoblotted for HA-tagged GSK3β. Plasmids were also transfected into MLE-12 cells and after 48 h of culture, cells were treated with proteasome inhibitor MG132 (20 µM) to allow accumulation of polyubiquitinated proteins. Lysates were immunoprecipitated for HA-GSK3β and immunoblotted with antibody for K48-linked ubiquitin. Lysates from a HEK293 expression library of over 30 F-box proteins were immunoblotted for endogenous GSK3β. Plasmid expressing histidine (V5)-tagged FBXO17 was also transfected into MLE-12 cells. Lysates were prepared after 48 h and immunoblotted for GSK3β.

**Results:** We identified lysine 183 as the primary acceptor site for K48-linked ubiquitin chains in GSK3β. K183R mutant GSK3β protein had a longer half-life and significant reduction in polyubiquitination than wild-type or K205R-GSK3β. Finally, we identified FBXO17 as a subunit of an SCF E3 ubiquitin ligase complex that targets GSK3β for polyubiquitination and proteasomal degradation in lung epithelial cells.

**Conclusion:** Our study characterizes a previously unknown mechanism for GSK3β degradation by the proteasome. We have identified FBXO17 as a subunit of an SCF E3 ligase complex that targets GSK3β. Future studies will focus on characterizing how FBXO17 modulates inflammation in lung epithelial cells. Our data suggest a critical role for the ubiquitin-proteasome pathway in regulating active and inactive pools of GSK3β which may influence the severity of lung inflammation.
Introduction: Innate immune signaling is central to lupus pathogenesis. Specifically, we and others have shown that the MyD88 signaling pathway is necessary to promote SLE in multiple murine models, with global deletion ameliorating disease and B-cells specific deletion abrogating most features of disease. Previously, we identified two upstream activators of MyD88 activation, which modulated disease in the MRL.Faslpr model of SLE. These activators/receptors are endosomal TLRs, TLR9 and TLR7. Surprisingly, despite being a "pro-inflammatory" innate immune receptor, TLR9 deficiency in lupus prone MRL.Faslpr mice exacerbates clinical manifestations including reduced lifespan and more severe nephritis, despite lacking anti-nucleosome (anti-DNA) antibodies; while TLR7 deficiency dominantly ameliorates disease. Similar regulatory roles for TLR9 have been identified in multiple other lupus models. The mechanisms by which TLR9 suppresses rather than promotes autoimmunity are unclear. We hypothesized that TLR9 has cell-specific functions and may suppress via activity in specific cell types.

Methods: We created two novel murine strains: a conditional TLR9 knock-out (Tlr9flox) and a conditional TLR9 overexpression allele (rosa26-flox-stop-Tlr9). Both were crossed onto lupus prone backgrounds with a B cell specific (CD19) Cre allele, then aged and analyzed for clinical manifestations including nephritis, dermatitis, lymphoproliferation, and antibody formation as well as immune activation.

Results: Strikingly, B-cell specific deletion of TLR9 exacerbated disease, similar to the complete knockout, exhibiting increased proteinuria (p<0.05) and nephritis (p<0.05) with loss of anti-nucleosome antibodies (p<0.001). In the reciprocal experiment, we assed the effects of TLR9 overexpression specifically in B cells. The rosa26-flox-stop-Tlr9 construct resulted in an ~2 fold overexpression of TLR9 in B cells, with a concomitant increase in function. When TLR9 was overexpressed only in B cells, we found that disease was ameliorated in two different models of SLE, MRL.Faslpr and B6.Fcgr2b−/−.Yaa,. There was reduced renal disease including proteinuria (p<0.05) and nephritis (p<0.05), but only modest alterations in autoantibodies with a 2 fold reduction in anti-RNA antibodies (p<0.05).

Conclusion: These data, in which we manipulate TLR9 expression in both directions, together indicate B cell expression of TLR9 accounts for a substantial proportion of the known TLR9 regulatory effect. To our knowledge this is the first data to show that TLR9 overexpression can be protective, and given its significant ameliorative effect, TLR9 overexpression in B cells alone may represent a potential therapeutic strategy.
**23-B Poster:**  T cell exhaustion in Lupus Nephritis: A key to Understanding Autoimmunity and the Adverse Effects of Checkpoint Blockade

**Presenter:** Jeremy Tilstra, Fellow  
Rheumatology and Clinical Immunology  
**Research Interest:** Bench

**Mentors:** Mark Shlomchik MD, PhD  
**Funding Source:** T32

**Authors:** Jeremy Tilstra MD, PhD, Lindsay Avery BS, Ashley Menk BS, Larry Kane PhD, Greg Delgoffe PhD, Mark Shlomchik MD, PhD

**Introduction:** T cell exhaustion is a mechanism of peripheral tolerance, which has been described in the setting of tumor immunology and chronic viral infection. Reinvigoration of these exhausted T cells has been the target of recent cancer trials, using PD-1 and CTLA-4 checkpoint blockade. Notably, these therapies cause unique adverse events, which resemble autoimmunity. Furthermore, features of the tumor microenvironment required for exhaustion, chronic inflammation and persistent antigen exposure, are recapitulated in the setting of autoimmunity. Thus we hypothesize that autoimmunity is the adaptive/evolutionary etiology for T cell exhaustion that has been maladapted by cancer and chronic viral infections to evade the immune system. Herein, we explore whether renal T cell infiltrates in a murine model of lupus nephritis exhibit the exhaustion phenotype.

**Methods:** T cells were isolated from lupus prone mice, and kidney infiltrating T cells (KITs) were compared to T cells isolated from matched spleens and non-lupus control spleens. Exhaustion markers, cytokine production, glucose uptake, and mitochondrial activity were assessed by flow cytometry. Metabolic stress testing was performed using a Seahorse XF analyzer.

**Results:** KITs from lupus prone mice were remarkable similar to exhausted T cells described in the setting of chronic viral infection and tumor infiltration. Not only did KITs have cell surface markers of exhaustion including PD-1, Lag3, Tim-3 and 2B4, but they were functionally inert with reduced cytokine production and lacked a proliferative capacity. Further, KITs exhibited a suppressed metabolic profile with limited glucose uptake and suppressed mitochondrial function. Moreover, we show that PD-L1, an important mediator of T cell exhaustion phenotype, is overexpressed in the kidneys of lupus prone mice with nephritis compared to pre-nephritic mice.

**Conclusion:** In all, these data are the first to define a novel role for T cell exhaustion in the setting of autoimmunity. This suggests that the kidney is attempting to suppress infiltrating T cells using exhaustion as a mechanism of peripheral tolerance. Further, these findings may explain why so many cancer patients treated with checkpoint blockade exhibit autoimmune like side effects; namely by reinvigorating suppressed auto-reactive cells in the periphery. The data supports our hypothesis that T cell exhaustion may be evolutionarily adapted to prevent autoimmunity and maladaptive in the setting of cancer. Further targeting T cell exhaustion may represent a potential therapeutic strategy for treatment of autoimmune disease.
**Introduction:** Sickle cell disease (SCD) is an autosomal-recessive-genetic disorder, which leads to red blood cell sickling and hemolysis. Systemic vaso-occlusive crisis (VOC) is the predominant pathophysiology requiring emergency medical care by SCD patients. 10-20% of SCD patients hospitalized with VOC tend to develop acute chest syndrome (ACS), a type of lung injury within next few days, suggesting a role for pulmonary vaso-occlusion in ACS. This epidemiology also provides a window for therapeutic intervention provided treatments to prevent vaso-occlusion exist. The cellular, molecular and biophysical mechanism of pulmonary vaso-occlusion has just started to unfold and a profound understanding is needed for the development of effective therapies. Our recent findings using quantitative fluorescence intravital lung microscopy (qFILM) revealed that lung vaso-occlusion is enabled by the entrapment of embolic neutrophil-platelet aggregates in the pulmonary arterioles of transgenic humanized SCD mice. Neutrophil extracellular traps (NETs) are web-like structures of decondensed nuclear DNA decorated with citrullinated-histones and neutrophil granule proteins. NETs are released by activated neutrophils under inflammatory conditions and are known to possess pro-inflammatory and pro-thrombotic properties.

**Methods:** Mice: Townes knock-in humanized SS (ha/ha:βS/βS) and AS (ha/ha:βA/βS) mice were used as SCD and control mice, respectively. AS mice are sickle cell trait mice. qFILM and analysis: Lung microcirculation was monitored using multi-photon excitation enabled quantitative fluorescence intravital lung microscopy (qFILM).

**Results:** Our initial findings using qFILM suggest that systemic challenge with hemin or oxy-hemoglobin (Oxy-Hb) triggers vaso-occlusive crisis in SCD mice, which results in sequestration of neutrophil-platelet aggregates and formation of NETs in the pulmonary arterioles of SCD mice.

**Conclusion:** Systemic challenge with erythroid eDAMPS, hemin and Oxy-Hb triggers pulmonary vaso-occlusion in SCD mice. Pulmonary vaso-occlusion in SCD mice is mediated by entrapment of neutrophil-platelet aggregates in precapillary arteriolar bottlenecks at the junction of pulmonary arterioles and capillaries. Pulmonary vaso-occlusion is associated with formation of NETs within the pulmonary arterioles of SCD mice.
Poster Abstracts

25-B Poster: EMT transcription factor TWIST1 mediates resistance to EGFR inhibitors in EGFR-mutant non-small cell lung cancer

Presenter: Zachary Yochum, Graduate Student
Research Interest: Bench Hematology/Oncology

Mentors: Timothy Burns MD, PhD
Funding Source: F30

Authors: Zachary Yochum BS, Hailun Wang PhD, Jessica Cades PhD, Suman Chatterjee PhD, Susheel Khetarpal, Eric Huang MS, Phouc Tran MD, PhD, Timothy Burns MD, PhD

Introduction: Recent advances in the treatment of non-small cell lung cancer (NSCLC) stem from the paradigm shift of classifying patients into subtypes based upon the presence of distinct molecular drivers. Subsets of patients, such as those with EGFR mutations and ALK translocations, have dramatic responses in their tumors to tyrosine kinase inhibitors (TKIs). Unfortunately, therapeutic resistance is inevitable. For EGFR-mutant NSCLC, there are multiple described mechanisms of resistance to EGFR TKIs, including epithelial-mesenchymal transition (EMT). We have previously demonstrated that the EMT-transcription factor, TWIST1, is required for oncogene-driven NSCLC tumorigenesis, including for EGFR-mutant NSCLC. Here, we investigated the role of TWIST1 in EMT-mediated resistance to EGFR TKIs.

Methods: TWIST1 and BIM were silenced with shRNA. NSCLC cell lines were created that doxycycline-inducibly overexpressed TWIST1. Viability was assessed via MTS assay and apoptosis was assessed via immunoblotting and cleaved-caspase 3/7 staining. A mutant Egfr/Twist1 transgenic mouse model of lung cancer was utilized to study erlotinib resistance in vivo.

Results: We observed that genetic or pharmacologic inhibition of TWIST1 resulted in growth inhibition in EGFR-mutant NSCLC cell lines and apoptosis in a subset of these lines. Interestingly, TWIST1 overexpression in EGFR-mutant NSCLC cell lines led to EGFR TKI resistance. Conversely, knockdown of TWIST1 in an erlotinib resistant EGFR-mutant NSCLC cell line restored erlotinib sensitivity. We found that TWIST1 mediates resistance to EGFR TKIs through suppression of apoptosis possibly through decreasing the expression of the pro-apoptotic Bcl-2 member, BCL2L11 (BIM). We observed that TWIST1 knockdown increased BIM levels, while TWIST1 overexpression decreased BIM expression. TWIST1-mediated resistance was overcome by treatment with the BCL-2/BCL-XL inhibitor, ABT-737. Knockdown of BIM recapitulated the resistance seen following TWIST1 overexpression, suggesting that TWIST1 suppression of BIM is a mechanism through which TWIST1 leads to EGFR TKI resistance. To explore the role of TWIST1 in modulating EGFR inhibitor sensitivity in vivo, we used an inducible EGFR-mutant transgenic mouse model, CCSP-rtTA/tetO-EGFRL858R (CE), which expresses EGFRL858R in the lung and a EGFR-mutant/Twist1 transgenic model, CCSP-rtTA/tetO-EGFRL858R/Twist1-tet07-luc (CET), which expresses both Twist1 and EGFRL858R in the lung. CET mice had a significantly increased tumor burden, decreased apoptosis and a decreased overall survival compared to CE mice following erlotinib treatment.

Conclusion: TWIST1 overexpression leads to EGFR TKI resistance by suppressing EGFR TKI-induced apoptosis through suppressing BIM expression. Future studies aim to establish the mechanisms of TWIST1 suppression of BIM expression and determine if our TWIST1 inhibitor, harmine, is effective in overcoming EMT-mediated resistance.
**26-B Poster:** PTEN-induced putative kinase 1 modulates opening of the mitochondrial permeability transition pore through phosphorylation of adenine nucleotide translocase 2 and 3

**Presenter:** Daniel Zank, Fellow
Pulmonary, Allergy and Critical Care Medicine

**Research Interest:** Bench

**Mentors:** Ana Mora MD

**Funding Source:** R01 HL131789-01 (Mora)

**Authors:** Daniel Zank MD, Marta Bueno PhD, Erin Steer PhD, Charleen Chu MD, Ana Mora MD

**Introduction:** Idiopathic pulmonary fibrosis (IPF) is a progressive, lethal form of interstitial lung disease, and while the cause remains unclear, more continues to be learned about the cellular and molecular processes associated with the development of IPF, including the potential role of dysfunctional mitochondria in the pathology of IPF. Our lab has previously demonstrated that type II alveolar epithelial cells from IPF lungs have low expression of PTEN-induced putative kinase 1 (PINK1), a serine-threonine kinase that functions in mitochondrial quality control. PINK1 deficiency is associated with accumulation of dysfunctional mitochondria characterized by swelling, loss of cristae, reduced mitochondrial membrane potential (?m), and increased release of mitochondrial DNA (mtDNA). These mitochondrial alterations are compatible with increased opening of the mitochondrial permeability transition pore (mPTP). Adenine nucleotide translocase (ANT) 2 and 3 are inner mitochondrial membrane proteins expressed in lung that exchange ADP and ATP across the membrane and are proposed to be either a component of the mPTP or a critical regulator of it. We propose that PINK1 asserts a regulatory influence on ANT2/3 affecting opening of the mPTP.

**Methods:** A549 human lung alveolar epithelial cells were transfected with siPINK1 and/or siANT2/3 in the presence or absence of mPTP modulators. ?m was measured by JC-1 staining and mPTP opening was determined using a calcein-cobalt assay. Detection of mtDNA release in the cell supernatant was performed by qPCR. Interaction between PINK1 and ANT2/3 was tested by co-immunoprecipitation (co-IP).

**Results:** PINK1 knock down in A549 cells showed increase in mPTP opening, reduction of the ?m, and release of mtDNA into the cell supernatant. Mitochondrial depolarization induced by tunicamycin, which reduces PINK1 transcription, was reversed by overexpressing PINK1. Co-IP revealed protein interaction between PINK1 and ANT2/3. Furthermore, phosphorylation of ANT2/3 was present in cells expressing PINK1 but not in PINK1 knockdown cells. Finally, A549 cells transfected with siANT2/3 showed reduced mtDNA release in the setting of reduced expression of PINK1.

**Conclusion:** PINK1-deficient A549 cells have reduced mitochondrial membrane potential, increased opening of the mPTP, and increased mtDNA release. This occurs in the absence of ANT2/3 phosphorylation. These findings suggest that PINK1 is necessary for ANT2/3 phosphorylation, and that ANT2/3 phosphorylation prevents opening of the mPTP. Manipulation of this pathway may offer a mechanism for regulating mPTP opening as well as a potential therapeutic target to abrogate mitochondrial dysfunction in the development of fibrosis in IPF.
**27-B Poster:** The Utility of Adrenal Venous Sampling for Guiding Surgical Management in Patients with Bilateral Adrenal Enlargement and ACTH-independent Cushing's Syndrome

**Presenter:** Runa Acharya, Fellow  
Endocrinology and Metabolism

**Research Interest:** Clinical

**Mentors:**  
Sue Challinor MD, Linwah Yip MD, Rupal Bandi MD

**Funding Source:** None

**Authors:** Runa Acharya MD, Mashaal Dhir MD, Linwah Yip MD, Rupal Bandi MD, Sue Challinor MD

**Introduction:** Management of the rare patient with bilateral adrenal enlargement (BAE) and ACTH-independent hypercortisolism (AIHC) is challenging. Adrenal venous sampling (AVS) has been reported in one single institutional series (n=10) as a technique to localize which adrenal gland is producing excess cortisol. Other studies have shown that unilateral adrenalectomy of the largest adrenal nodule improves hypercortisolism. The aim of the current study was to investigate the utility of AVS in guiding management of patients with BAE and AIHC.

**Methods:** A retrospective review of all patients with AIHC and BAE who underwent AVS at our institution between 2008-2016 was performed after QAQI-IRB approval. Diagnostic criteria for AIHC included low basal ACTH and at least 2 concordantly positive screening tests for Cushing's syndrome based on 2008 clinical practice guidelines. All patients had CT findings of BAE. The protocol for AVS and interpretation of AVS results was based on previously published criteria. Adrenal vein (AV) to peripheral vein (PV) cortisol gradients were categorized as >6.5 = cortisol-secreting adenoma and < 3.3 = nonfunctioning adenoma. If the side-to-side AV cortisol lateralization ratio (CLR) was 2.3 unilateral cortisol hypersecretion was diagnosed and if CLR was 2 then bilateral cortisol hypersecretion was present.

**Results:** Eight patients with AIHC and BAE underwent AVS. Median age was 61 years and all were women. Mean BMI was 33.2. Imaging with CT demonstrated bilateral adenomas in 4, unilateral adenoma with contralateral hyperplasia in 1 and bilateral hyperplasia or lobulated enlarged nodules in 3 patients. Successful catheterization was achieved in 7 patients. Six patients demonstrated bilateral cortisol hypersecretion based on AV/PV gradients and CLR. One patient did not meet criteria for cortisol hypersecretion from either gland despite positive biochemical screen for hypercortisolism on serum and salivary tests. Three patients (50%) had unilateral adrenalectomy of the larger adrenal and AVS cortisol levels were higher on the resected side. Two patients (33%) required bilateral adrenalectomy.

**Conclusion:** All patients in our series who underwent successful AVS had bilateral cortisol hypersecretion. Our results are in contrast to a prior study and the utility of AVS in patients with AIHC and BAE needs further investigation. Surgical resection of the larger adrenal gland without AVS remains a valid option. Given the limited sample size, data from larger numbers of patients are needed before AVS can be recommended as essential for guiding surgical management.
Introduction: Hypoglycemia occurring in the hospital setting is associated with more frequent readmissions and higher mortality following discharge in patients with diabetes, although the reasons for this are not known.

Methods: Based on the assumption that patients with hypoglycemia unawareness (HU) experience more adverse outcomes than those with hypoglycemia awareness (HA), we examined frequency of recurrent hypoglycemia, ER visits, re-hospitalization, and mortality at one year among non-critically ill insulin treated patients with diabetes identified as HA (n = 23) or HU (n = 32) based on a validated Hypoglycemia Symptom Scores (HSS) obtained within 24 hours of experiencing a verified BG <70 mg/dl.

Results: Follow-up data was obtained for 15 HA and 25 HU patients at 6-12 months following the index hospitalization. No differences were observed in baseline clinical characteristics for age (HA vs. HU: 63.4 + 10.1 vs. 65.2 + 10.5 y), sex (53 vs. 44% male), race, BMI (32.5 + 9.3 vs. 32.8 + 11.8 kg/m2), A1C (9.8 + 1.6 vs. 9.9 + 1.7%), or index BG (52 + 10 vs. 57 + 7 mg/dl). Autonomic (6.5 + 4.5 vs. 0.4 + 1.6), neuroglycopenic (4.5 + 4.6 vs. 1.2 + 2.2), and total HSS were lower in HU (all p < 0.01). At follow-up, 3 HA and 2 HU patients were deceased. Among the remaining subjects, 8/12 HA and 10/23 HU reported recurrent hypoglycemia with 1-8 episodes/month with mean reported nadir BG 50 + 12 vs. 58 + 10 mg/dl (p = 0.08). 1 HA and 3 HU subjects indicated the need for assistance. 9/12 HA and 9/23 HU subjects reported 2.0 + 2.3 vs. 2.6 + 1.9 ER visits (p = 0.32); 6/12 and 7/23 reported 2.0 + 3.0 vs. 2.5 + 1.5 re-hospitalizations (p = 0.2); and 4/12 and 5/23 reported experiencing = 1 falls (p= 0.4).

Conclusion: In summary, although the number of subjects available for follow-up in this investigation was small, more than 50% of patients reported recurrent hypoglycemia events following hospital discharge. No differences were observed between patients with HA vs. HU suggesting that the occurrence of hypoglycemia alone rather than HU poses risk for adverse outcomes, with 51% reporting 1-8 ER visits, and 37% reporting 1-8 re-hospitalizations in the 12 month period following the index hospitalization. These findings are consistent with the reported high frequency of re-hospitalizations among people with diabetes reported in larger retrospective analyses, and reinforce recommendations to modify glycemic management strategies to minimize risk for these events in high risk individuals.
Introduction: While cardiac rehabilitation (CR) programs such as home-based (HB) and hybrid (H) are widely touted for convenience and adherence, it remains unclear which patients are best suited for these models. Current standards of risk stratification are modeled for traditional facility-based (FB) CR and based primarily on cardiovascular (CV) risk. We evaluated baseline differences between patients enrolling in HB vs. H vs. FB vs. No-CR.

Methods: In a retrospective quality improvement analysis of 295 Veterans assessed for CR we evaluated comorbidities, distance to facility, physical function (6 minute walk distance [6MWD], gait speed [GS], tandem stand [TS]), and health literacy (Rapid Estimate of Adult Literacy in Medicine [REALM]) to compare Veterans enrolled in HB, H, FB, and No-CR.

Results: Patients enrolling in HB care tended to reside farther from facilities (86 vs 26 miles, p=<0.01). FB-CR was highly preferred by HF patients than HB (22% vs 1.9%, p=<0.01, respectively), while post-CABG patients were more likely to enroll in HB or H-CR. Patients enrolling in HB/H CR had better physical function than patients in FB-CR (6MWD 354 ± 77.7 / 334 ± 76.9 vs 275 ± 94.3, p=<0.01, respectively). Patients that did not enroll in any CR exhibited significantly poorer health literacy (HB 6.22 ± 1.58, H 6.22 ± 1.53, FB 5.82 ± 1.94, No-CR 3.84 ± 3.40 p=<0.01, respectively). HF, depression, and T2DM differed in there distribution of CR programs, but other comorbidities (CKD, CAD, COPD, HTN) had little impact on treatment pathways.

Conclusion: Functional metrics constituted the most significant differences between patients who attended HB/H vs. FB, whereas CV risk is the more significant factor between HB vs H. These data suggest that further refinement of risk assessment for HB/H-CR may be warranted to determine minimum thresholds of functional capacity that enable HB/H-CR to be feasible and successful.
31-B Poster: Follicular Lymphoma as the Presenting manifestation of Common Variable Immune deficiency in an Adult Patient

Presenter: Jennifer Boeckman, Fellow
Research Interest: Clinical Pulmonary, Allergy and Critical Care Medicine

Mentors: Merritt Fajt MD
Funding Source: None

Authors: Jennifer Boeckman DO, Andre Petrov MD, Merritt Fajt MD

Introduction: Common variable immunodeficiency (CVID) is the most common significant primary adult immunodeficiency. Historically infections were the most important predictor of morbidity and mortality; however, with the use of intravenous immunoglobulin (IVIG) and prophylactic antibiotics, lymphoproliferative disorders and malignancies are now the leading causes of mortality. There has been slow progress in the molecular understanding of CVID. To date, only been a few single gene mutations have been identified which do not account for the majority of CVID cases. There is an eleven fold increase in mortality if a patient has CVID associated with a certain phenotype. We present a case of CVID with multiple complications of this disease, including follicular lymphoma, nodular regenerative hyperplasia, severe restrictive lung disease, recurrent infections and cytopenia.

Methods: na

Results: The patient is a 37 year old male with past medical history of follicular lymphoma in 1999. He was later diagnosed with CVID in 2013 and was started on IVIG. On IgG replacement, infection frequency decreased. He began experiencing dyspnea on exertion. Pulmonary function tests were done shortly after and have shown a progressive decline in both the FEV1 and FVC. Imaging of the chest showed widespread parenchymal nodularity and mediastinal lymphadenopathy. Repeated biopsy of the lymph nodes was negative for malignancy. In September 2016, liver biopsy showed nodular regenerative hyperplasia and he was hospitalized for hemoptysis, CBC showed a decrease in all cell lines. He was started on Rituximab with improvement in his pulmonary function and lymphadenopathy on CT scan of the chest. He continues on weekly subcutaneous IgG replacement and antibiotic prophylaxis.

Conclusion: Treatment with IgG replacement has increased the lifespan for most CVID patients, but a small subset have other disease complications that affect morbidity and mortality. In this subset of patients, additional treatment is needed as well as close monitoring of all clinical symptoms. There are small studies that show a benefit to combination chemotherapy is some of these cases. Currently, only a small number of single gene disorders have been discovered that do not explain a majority of CVID cases but there have been studies showing immune dysregulation and abnormalities in certain biomarkers. However, further research is needed to better understand pathological mechanisms of these shared forms of immune dysregulation which may ultimately lead to additional therapies for the CVID patient subset with multiple complications.
32-B Poster: Antibiogram-a-rama: Comparing Antibiograms to Guide Providers in the Treatment of UTI

Presenter: Christina Bungo, Fellow
Geriatric Medicine

Research Interest: Clinical

Mentors: None

Funding Source: None

Authors: Christina Bungo DO, John Naumovski MD, Keisha Ward MD, Debbie McDonald RN, David McKnight PharmD

Introduction: Antibiotic stewardship in long-term care facilities is a frequent target for quality improvement due to wide antibiotic misuse. UTIs are the most common reason antibiotics are prescribed in this setting. Previous studies have demonstrated inappropriate use of antibiotics in UTI, particularly overuse of fluoroquinolones, despite CDC recommendations to use other agents as first-line therapy. Choosing an appropriate antibiotic for LTC residents can be a difficult task. Prescribers face many limitations, including routes of administration, side effects, and local susceptibility patterns. The objective of this QI project was to compare antibiograms from the community to a LTC facility to guide prescribers in choosing antibiotics for treatment of UTI.

Methods: This QI project took place at a 159-bed nursing facility. An antibiogram was created using urine culture/sensitivities from the previous 12 months. This was compared to antibiograms from two large local community hospitals. A list of appropriate antibiotics was compiled, with particular emphasis placed on oral antibiotics with less severe side-effect profiles in the elderly.

Results: There were 78 urine cultures with a predominant organism during the 12-months of observational data. The average age of residents was 86 years old, and 82% were female. The most common bacteria were E. coli (55%), K. pneumonia (18%), and P. mirabilis (14%). Other pathogens were present in fewer than 4 cultures each. Susceptibilities for the most common bacteria were compiled into an antibiogram. In comparison to antibiograms of local hospitals, LTC had lower rates of Pseudomonas and MRSA. Of the most common bacteria, susceptibility patterns were similar among the antibiograms. Cephalosporins were the best first-line therapy for UTI in our facility, followed by TMP-SMX and fluoroquinolones.

Conclusion: This QI project sought to improve antibiotic use by comparing data sources for local bacteria. By developing a site-specific antibiogram and comparing to larger local antibiograms, we produced a reliable list of first-line agents for providers at our facility. Future challenges will include updating recommendations while monitoring for the development of new resistance patterns.
**Introduction:** Efforts to improve antibiotic prescribing have become essential due to increased bacterial resistance and decreased antibiotic formulation. Long term care (LTC) facilities play a unique role in antibiotic overuse, as studies have found that 47-79% of LTC residents receive antibiotics at these facilities per year. UTIs are the most common reason for antibiotics in LTC, and fluoroquinolones are among the most commonly prescribed. In antibiograms taken from the two largest hospital systems in Pittsburgh, resistance rates to ciprofloxacin were as high as 31%. In addition to rising resistance, the side effects of quinolones, including risk of tendon rupture and QTc prolongation, create further risk for the elderly. An assessment of prescriptions from our facility revealed that a large percentage of UTIs are treated with fluoroquinolones as first line therapy, despite CDC recommendations to use other agents. Therefore, to improve prescribing habits, a strong alternative choice of empiric antibiotic and educational initiatives are necessary.

**Methods:** The setting for this QI project is Charles Morris Center for Rehab and Nursing, a 159-bed nonprofit nursing facility. Clinical symptoms, urinalysis, culture, and antibiotic choice were analyzed from PA-PSRS over 12 months. Educational initiatives were implemented to provide awareness of high resistance rates to fluoroquinolones. Monthly reports of urine pathogens, culture sensitivity, and antibiotic use were reviewed and shared with providers. The frequency of fluoroquinolone prescriptions were monitored following the interventions.

**Results:** There were 73 reported UTIs during the initial 12-months of observational data. The average age of participants was 86 years old, and 70% were female. Of the 95% that had a culture sent, 58% grew E. coli. Prior to the intervention, fluoroquinolones were the most frequently prescribed antibiotics (49.3%). Other antibiotics used included trimethoprim/sulfamethoxazole (9.6%), cephalosporins (6.8%), and nitrofurantoin (2.7%). Post-intervention data is pending and will be available at the time of presentation.

**Conclusion:** This ongoing QI project aims to decrease overprescription of fluoroquinolones in a LTC facility. Fluoroquinolones were the most frequently prescribed first-line therapies in the preliminary data, despite high resistance rates, risk of adverse events, and published guidelines recommending the use of other agents. This project used educational interventions, including journal articles and monthly review of prescribing habits, to reinforce recommended alternatives. Analysis of prospective data is ongoing but suggests that this is a useful technique for changing the prescribing culture of a LTC facility. With fluctuating bacterial resistance in LTC, this intervention could serve as a model to maintain appropriate antibiotic use now and into the future.
Introduction: Patients in Cardiac Rehabilitation (CR) vary significantly with respect to comorbidities. Depression and/or anxiety (DA) are risk factors for cardiovascular disease (CVD), and also increase risk for secondary events once CVD is established. Whereas CR includes home-based (HB-CR) as well as facility-based (FB-CR) options, little is known about whether DA status influences enrollment in HB-CR vs FB-CR programs. PURPOSE: We compared patients with DA and with No-DA (NDA) in respect to HB-CR vs. FB-CR enrollment in a Veterans Healthcare System (VHS) center which offered both programs.

Methods: METHODS: In a quality improvement project we evaluated 239 Veterans at baseline before beginning CR. Patients were evaluated for medical and physical risks to determine a recommendation for either FB-CR or HB-CR. Patients who demonstrated moderate or high medical or physical risk were advised to pursue FB-CR; however patients ultimately made the decision on whether to enroll in CR. A patient deemed moderate or high medical or physical risk would not be allowed to choose HB-CR, but this risk assessment was independent of DA status. At baseline patients completed the 8-item Personal Health Questionnaire Depression Scale (PHQ-8) and the Generalized Anxiety Disorder 7-item scale (GAD-7). 6 Minute Walk Distance (6MWD) and Gait Speed (GS) were also assessed as metrics of physical function.

Results: RESULTS: Patients with baseline depression (PHQ-8=10) and/or anxiety (GAD-7=10) (N=56) were more likely to enroll FB-CR (67.9% vs. 48.6%, p=0.028) than NDA (N=183) patients. Conversely, NDA patients were more likely to enroll HB-CR (24.6% vs. 8.9%). Patients with DA also had lower 6MWD (278 ± 100 vs. 314 ± 92.5, p=0.0179) and GS (1.08 ± 0.28 vs. 1.21 ± 0.29, p=0.0068) than NDA.

Conclusion: CONCLUSIONS: Veterans with DA are more likely to enroll in FB-CR and have lower baseline values of physical function than Veterans with NDA. However, it is unknown if and how DA patients are better served with FB-CR. Future studies are indicated to clarify utility of FB- vs. HB- CR for DA as HB-CR programs continue to proliferate in the VHS and in many cases now supplant FB-CR options.
**Introduction:** The overall goal of the research is to develop neutrophil-specific PET tracers targeting formyl peptide receptor type 1 to provide detailed information about tuberculosis (TB) granulomas. We originally performed PET imaging studies with antagonist 64Cu-CBTE1A1P-PEG12-cinnamoyl-Phe-(D)Leu-Phe-(D)Leu-Phe(cFLFLF). Although this tracer showed high uptake in the Complete Freund's Adjuvant (CFA) paw inflammation mouse model, it also showed high liver uptake due to the lipophilicity of the peptide structure. To overcome this problem, we developed a new antagonist, replacing Phe in the 1 and 3 positions to 4-Benzoyl-L-phenylalanine (Bpa) and 3-cyclohexyl-L-alanine (Cha), respectively. In addition, we conjugated the NODAGA chelator to PEG12-Cinnamoyl-(D)Bpa-(D)Leu-(D)Cha-(D)Leu-Phe(cBLCLF)\[1\] for 64Cu labeling.

**Methods:** The final compound NODAGA-PEG12-cBLCLF was successfully synthesized as confirmed by ESI mass spectrometry and HPLC. For 64Cu labeling to NODAGA-PEG12-cBLCLF, 4 nmol of NODAGA-PEG12-cBLCLF was reacted with 2 mCi of Cu-64 in 0.1 M ammonium acetate buffer (pH 4.1) for 10 min at 70° C. For the paw inflammation model, mice (6 to 8 weeks old) were subcutaneously injected with CFA (50 µL) in the right paw. Mice were imaged 24 hours after CFA injection at 6 and 18 h post-tracer injection.

**Results:** The radiolabeling efficiency was 99%. 64Cu-NODAGA-PEG12-cBLCLF was >98% stable in PBS at 37° C out to 6 h. The CFA paw inflammation mouse model showed uptake of 64Cu-NODAGA-PEG12-cBLCLF in the site of inflammation. The SUVmean of the inflamed site was 2.0 ± 0.12 at 6 h, and 2.0 ± 0.43 at 18 h, respectively. Inflammation/muscle ratios are 6.5 at 6 h, and 6.7 at 18 h, respectively. The inflamed paw/normal paw ratios are 5.4 at 6 h, 5.8 at 18 h, respectively.

**Conclusion:** Our group has developed a novel neutrophil-targeted PET imaging probe, 64Cu-NODAGA-PEG12-cBLCLF. This tracer is taken up in sites of inflammation caused by CFA injection in the hind paw compared to the non-inflamed paw.
**Poster: Long Term Risk of Colorectal Cancer after Detection of Adenomatous Polyps**

**Presenter:** Benjamin Click, Fellow  
**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition  
**Mentors:** Robert Schoen MD  
**Funding Source:** None  
**Authors:** Benjamin Click MD, Maryam Doroudi PhD, Tom Hickey BS, Paul Pinsky PhD, Robert Schoen MD

**Introduction:** Individuals with adenomatous polyps are advised to undergo colonoscopy (CS) surveillance to prevent subsequent colorectal cancer (CRC), but the relationship between adenomas at CS and long-term CRC incidence is unclear.

**Methods:** Subjects undergoing screening flexible sigmoidoscopy in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial with findings of a polyp and subsequent CS were followed for CRC incidence for 13 years or until death or loss to follow-up. CS findings were categorized as advanced adenoma (AA) (=1 cm, or tubulovillous or villous histology, or high grade dysplasia), non-advanced adenoma (NAA) (<1 cm and without advanced histology), or no adenoma (NA). Subjects with CRC on baseline CS were excluded. CRC incidence rates were compared using NA as the referent group.

**Results:** Of 15,935 eligible subjects who underwent CS, 2882 (17.8%) had an AA, 5068 (31.4%) had a NAA (=3 NAA n=572, 1-2 NAA n=4496), and 7985 (49.4%) had NA, and were followed for a median of 9.7 years. CRC incidence rates were 18.3, 6.8, and 5.7 per 10,000 PYO for AA, NAA, and NA subjects respectively. On multivariable proportional hazards modeling controlling for age, sex, aspirin use, and prior lower endoscopy, AA subjects were more likely to develop CRC compared to NA subjects (adjusted hazard ratio [AHR] 3.16; 95% confidence interval [CI] 2.1-4.8). Compared to subjects with NA, there was no significant difference in CRC risk with NAA (AHR 1.21; 95% CI 0.8-1.9); risk did not differ by number of NAA (=3 NAA: AHR 1.93; 95% CI 0.8-4.7; 1-2 NAA: AHR 1.11; 95% CI 0.7-1.8). In the AA and the NAA groups, there was no significant difference in CRC risk between years 5-10 compared to years 0-5 (RR 1.2; 95% CI: 0.5-1.7 for AA and RR 2.6; 95% CI: 0.9-5.6 for NAA). Surveillance CS utilization data was available for a subgroup of 3492 subjects with median follow-up of 9.0 years as part of an ancillary study of surveillance CS in the PLCO cohort. At 9 years, surveillance CS utilization was significantly higher in the AA group compared to NAA and NA (82.5% vs. 78.7% [p=0.008] vs. 69.9% [p<0.0001], respectively) and more AA subjects underwent adenoma removal than NAA and NA (40.4% vs. 33.2% [p<0.001] vs. 20.3% [p<0.001]). Subjects with 1-2 NAA had 8% more surveillance CS (78.1% vs. 69.9%, p=0.001) and 11% more adenoma removal (31.1% vs. 20.3%, p=0.001) compared to NA.

**Conclusion:** Having an advanced adenoma at baseline CS is associated with a three-fold increased long-term risk for incident CRC compared to subjects with no adenomatous findings, suggesting that ongoing surveillance CS is advisable for subjects with an AA. In contrast, there was no significant difference in CRC incidence between subjects with NAA and no adenomas, suggesting that surveillance for NAA may not be required.
**37-B Poster:** Patient management at a pulmonary hypertension center of comprehensive care improves clinical outcomes compared with non-specialty care.

**Presenter:** Aken Desai, Fellow Cardiology

**Research Interest:** Clinical Cardiology

**Mentors:** Stephen Chan MD

**Funding Source:** None

**Authors:** Aken Desai MD, Kevin Quinn MS, Adam Handen MS, Andrew Althouse PhD, Michael Risbano MD, Marc Simon MD, Belinda Rivera-Lebron MD, Michael Mathier MD, Oscar Marroquin MD, Stephen Chan MD

**Introduction:** The diagnosis and management of WHO Group 1 pulmonary arterial hypertension (PAH) has become increasingly specialized. The Pulmonary Hypertension Association has developed criteria to designate PH Centers of Comprehensive Care. We sought to evaluate whether delivery of care in this setting had an influence on outcomes.

**Methods:** The UPMC Clinical Analytics database was used to identify patients with at least one outpatient encounter from 2010 to 2014 (1,670,372 unique patients) that had a diagnosis of pulmonary hypertension in their medical records. This database includes the historical electronic health records compiled over the network of 22 UPMC-affiliated hospitals and practices in Western PA. Patients were divided into two groups: those managed at the UPMC Comprehensive PH Program (the Center) and those outside the Center. From this, we extracted hemodynamic data to find patients who met the criteria of PAH. Survival was assessed using Kaplan-Meier analysis and Cox proportional-hazards models.

**Results:** 536 patients cared for during the period of interest met the hemodynamic criteria for Group 1 PAH; 376 were seen at the Center vs. 160 outside. The Center group was younger (59.1 years old vs. 63), had a slightly higher left ventricular ejection fraction (52.8% vs. 50.9%), lower prevalence of diabetes, CHF, COPD, hypertension, and osteoporosis. The use of vasodilator therapy was higher (81.4% vs. 45%). One-year mortality was lower in the patients managed at the Center (11.3% vs. 23.1%). Multivariable analysis suggested that this association remained strong after adjustment for potential confounders (HR=0.58, 95% CI 0.43-0.80, p<0.01).

**Conclusion:** Patients diagnosed with Group I PAH managed at the UPMC Comprehensive PH Program were treated with pulmonary vasodilators more often and displayed a lower mortality. Limitations in this study that are being addressed include a lack of data from non-UPMC facilities as well as challenges defining objectively the functional status of patients and severity of illness.
**38-B Poster:** Impact of Testosterone Replacement Therapy (TRT) on Outcomes: Seven year Experience comparing Restrictive Policy adhering to Endocrine Society guidelines with Unrestricted Use

**Presenter:** Samaneh Dowlatshahi, Fellow  
**Research Interest:** Clinical Endocrinology and Metabolism

**Mentors:** R. Harsha Rao MD, Alexandra Clark MD  
**Funding Source:** None

**Authors:** Samaneh Dowlatshahi MD, Alexandra Clark MD, Erika Hoffman MD, Laura Potoski PharmD, Peter Perreiah PhD, R. Harsha Rao MD

**Introduction:** Studies report conflicting results for outcomes with TRT, extending, from a survival benefit, through no impact, to increased mortality. Such stark contradictions might be explained if outcomes are driven by variable pre-existing risk for Major Adverse Cardiovascular Events (MACE) in different studies. A framework for defining such pre-existing risk exists in the Endocrine Society (ES) guidelines for TRT, but it is not known if their use can affect MACE. The VAPHS Endocrine Division has followed a policy since 2008 that predates, but mirrors, ES guidelines for appropriate diagnosis and monitoring in restricting TRT to a low risk population, defined by

- **Comorbid Contraindications:**
  - **Absolute:** MACE in prior year (MI, active coronary artery disease, stroke, thromboembolic/peripheral vascular event), untreated obstructive sleep apnea, liver disease, prostate cancer, breast cancer
  - **Relative:** age > 65, MACE > 1y, PSA > 4, hematocrit > 50%

- **Diagnostic validation** by = 2 T levels at 8am by LC/MS/MS, with Total T (TT) < 200 ng/dl or calculated bioavailable T (cBAT) < 100 ng/dl
- **Goal T** 400-600 ng/dl
- **Monitoring:** T, Hct, PSA 3-6m after initiation

Since most TRT is prescribed without any constraints by primary care physicians (PCPs) at VAPHS, it provides a unique opportunity to compare outcomes with unrestricted TRT use versus TRT use constrained by ES guidelines.

**Methods:** Retrospective cohort study of veterans prescribed TRT at VAPHS, 2008-2014, (PCP n=582 [first-time n=431, renewal from elsewhere n=151]; ENDO n=125 [first-time n=101, renewal n=24]).

**Results:** PCPs were significantly less likely (all p<0.001) to diagnose hypogonadism with =2 T levels (PCP 217/431 [50.3%], ENDO 87/101 [86.1%]), by LC/MS/MS assay (PCP 149/431 [34.6%], ENDO 80/101 [79.2%]), at 7-9am (PCP 100/431 [23.2%], ENDO 53/101 [52.5%]), using strict criteria (Total T = 200, cBAT < 100: PCP 257/431 [60%] vs ENDO 79/101 [78%]). PCPs more often prescribed TRT (all p<0.001) at age = 65 (PCP 206/582 [35.4%], ENDO 20/125 [16%]), despite contraindications, both relative and absolute (PCP 388/582 [66.7%], ENDO 55/125 [44%]), and without proper monitoring within 6 mo (No TT: PCP 210/430 [48.8%], ENDO 14/104 [13.5%]; No Hct: PCP 213/430 [49.5%], ENDO 25/104 [24%]; No PSA: PCP 265/407 [65.1%], ENDO 32/83 [38.6%]). Despite longer TRT duration (PCP 23.4±0.9mos; ENDO 28.7±2.1, p=0.015), the ENDO cohort experienced a ~70% relative risk (RR) reduction in MACE (PCP 105/582 [18%]; ENDO 9/125 [7.2%], RR 0.31 [95% CI 0.15, 0.65], P=0.002).

**Conclusion:** A restrictive policy adhering to ES guidelines for TRT to exclude high risk patients and enforce strict diagnostic criteria with appropriate monitoring is associated with a lower risk of MACE.
**39-B Poster:** Glycemic excursions and bolus frequency with Insulin Pump Therapy

**Presenter:** Dinesh Edem, Fellow  
Endocrinology and Metabolism

**Research Interest:** Clinical

**Mentors:** Mary Korytkowski MD  
Maja Stefanovic MD, PhD

**Funding Source:** None

**Authors:** Dinesh Edem MD, Mary Korytkowski MD, Maja Stefanovic MD, PhD

**Introduction:** Insulin pump therapy (IPT) is an effective method for achieving glycemic control in people with insulin requiring diabetes. IPT allows flexibility in the frequency and timing of bolus insulin doses, which in some patients can lead to frequent insulin boluses (i.e. insulin stacking) that increase risk for hypoglycemia and hyperglycemia.

**Methods:** The goal of this study was to examine the associations between bolus frequency, glycemic control and variability; as well as the incidence and severity of mild (BG <70mg/dl) and severe hypoglycemia (BG <40 mg/dl); and hyperglycemia (BG >180 mg/dl) in adults using IPT. 2 weeks of de-identified pump data obtained at the time of a scheduled office visit were grouped according to <5 (Group 1: n=38) and =5 (Group 2: n=49) insulin boluses per day.

**Results:** No differences were observed for age (Group 1 vs 2: 47.4±15.8 vs 43.9±15.3 years), gender (42% vs 39% male), DM duration (29.2±14.2 vs 25.2±10.5 years), weight (82.2±15.6 vs 77.2±19.3 kg), BMI (28.7±5.1 vs. 26.8±4.9 kg/m2) or Creatinine (0.9±0.3 vs 0.9±0.2 mg/dl). Total daily insulin dose (49.1±18.2 vs. 45.8±24.4 units, p=0.49) was similar, but the percentage administered as bolus insulin was higher in Group 2 (43.8±15.3 vs. 50.4±10.4%, p=0.02). Group 2 administered more total boluses (3.5±0.9 vs 7.5±2.8, p=0.0001) both with (2.4±1.1 vs 4.0±1.8, p=0.0001) and without food (2.3±0.8 vs 3.2±1.4, p=0.0004). There were more manual overrides of the bolus wizard in Group 2 (0.5±0.8 vs 1.3±1.5, p=0.007). Group 2 patients monitored BG more frequently (3.8±2.1 vs 5.8±3.0, p=0.0007); had lower A1C (8.1±1.2 vs 7.4±1.0, p=0.004) and lower mean BG (200±50 vs 176±44 mg/dl, p=0.018) and experienced less hyperglycemia (49.6±23.6% vs 39.0±22.0% of BG readings, p=0.03) with more mild (3.0±4.0 % vs 5.1±5.2 % of BG readings, p=0.04) but not severe hypoglycemia (0.1±0.5 % vs 0.1±0.5 %, p=0.59) events. No differences were observed for glycemic variability (Coefficient of Variation for BG 39.4±7.9 vs 39.5±11.5, p=0.963).

**Conclusion:** Patients using IPT for glycemic control who bolus more frequently had better glycemic control with less hyperglycemia and more hypoglycemia. The introduction of sensor augmented pump therapy that automatically corrects basal insulin infusion rates according to glycemic excursions may more reliably guide adjustments of insulin with less risk for hypoglycemia and an improved safety profile.
**40-B Poster:** High utilizers of Condition Help: Demographic and medical characteristics of patients who repeatedly activate rapid response teams

**Presenter:** Elizabeth Eden, Fellow  
General Internal Medicine

**Research Interest:** Clinical

**Mentors:** Greg Bump MD,  
Allison Dekosky MD

**Funding Source:** None

**Authors:** Elizabeth Eden MD, Alison DeKosky MD, Laurie Rack MSN, Ling-wan Chen MS,  
Gregory Bump MD

**Introduction:** Patient activated rapid response teams have been implemented to improve patient safety and enhance patient engagement. The University of Pittsburgh Medical Center (UPMC) implemented a patient and family initiated rapid response system called Condition Help. Condition Help triggers a patient care liaison or administrator on duty along with a charge nurse to convene at the patient’s bedside to address concerns. A previously conducted analysis of 3.5 years of UPMC data revealed that nearly half of Condition Help events are activated by a small subgroup of patients, yet fewer than 6% of these events were categorized as safety concerns. Most of these calls were attributed to unsatisfactory pain control or other medical management issues. We sought to describe demographic and medical characteristics of those patients who frequently activate Condition Help, given the high utilization of resources required to address their concerns. It is critical to understand more about these patients, for potentially earlier identification and alternative interventions to better meet their needs.

**Methods:** Of the 240 patients who activated Condition Help at UPMC Presbyterian from January 2012 through July 2015, 43 patients called more than once, accounting for 46% of events (170 of 367). Charts were reviewed for repeat callers to collect basic demographic information including age, gender, race, marital status, employment status, and category of insurance. Documentation of substance use, comorbid psychiatric disease and primary medical diagnosis leading to inpatient admission were recorded.

**Results:** Most patients were female (72%), Caucasian (70%) and single (72%) with a mean age of 39 years (SD 12.8). On average members of this group were admitted 5.67 times per year (SD 5.4). 79% were unemployed or on disability and 21% were employed or retired. 58% had Medicaid or Medical Assistance, 32% had Medicare, and 10% had commercial insurance. Most patients used chronic opiates (77%), 16% used marijuana, and 12% used other illicit substances. Primary reason for admission was related to gastrointestinal complaints in 51%; of these 18% had inflammatory bowel disease and 18% had acute or chronic pancreatitis. 5% had sickle cell disease. Comorbid psychiatric illness was common with 82% of patients. 88% were discharged to home and the remainder were placed at either skilled nursing facilities or transferred to inpatient psychiatry.

**Conclusion:** Patients who repeatedly activate the Condition Help team demonstrate high medical resource utilization. Prevalence of unemployment and qualification for Medicaid and Medical Assistance indicate that they have limited income and resources. These data also show that most patients have chronic pain and comorbid psychiatric conditions. These data suggest that this group may benefit from early interventions targeting pain management and psychiatric care.
**41-B Poster:** Exposures to environmental pollutants and racial disparities in cardiovascular disease risk

**Presenter:** Sebhat Erqou, Fellow Cardiology

**Research Interest:** Clinical

**Mentors:** Steven Reis MD, Jane Clougherty PhD

**Funding Source:** None

**Authors:** Sebhat Erqou MD, Jane Clougherty PhD, Oladipupo Olafraniye MD, Aryan Aiyer MD, Kevin Kip PhD, Steven Reis MD

**Introduction:** The relationship between environmental air pollutants with clinical CVD risk factors, and their role in racial disparities have not been fully elucidated. We aimed to assess racial disparities in CVD risk in relation to urban air pollution exposures.

**Methods:** We used data from the Heart Strategies Concentrating on Risk Evaluation (HeartSCORE) study. Exposure to urban air pollutants was determined using land-use regression models derived from measures of particulate matter smaller than 2.5 microns aerodynamic diameter (PM2.5) and black carbon (BC) across the Pittsburgh metropolitan area. Cross-sectional correlations were assessed using linear regression models, adjusted for age, sex, smoking status, race, income and education status. Cox-regression was used to determine hazard ratios of CVD risk and all-cause mortality.

**Results:** Exposure estimates were built for 1,717 participants, of which 66% were females and 45% were Black; the mean (SD) age was 58 (8) years. Black individuals had significantly higher exposure to PM2.5 and BC compared to Whites that remained highly significant in fully adjusted model. In univariate model, PM2.5 was significantly associated with elevated systolic blood pressure, body mass index, blood glucose, Framingham reactive hyperemia index (fRHI, a measure of endothelial dysfunction), and interleukin 6 (IL6) levels. The association of PM2.5 with blood glucose and fRHI persisted in fully adjusted model. There were similar but weaker and statistically nonsignificant associations for BC. Exposure to PM2.5 was associated with increased risk of combined CVD and all-cause mortality outcome over a median follow-up of 8.3 years, after adjusting for CVD risk factors.

**Conclusion:** In a community-based cohort in Pittsburgh, we found racial disparities in exposures to urban air pollutants. Exposures to PM2.5 were independently associated with elevated blood glucose and worse endothelial function. PM2.5 was also associated with increased risk of combined CVD and all-cause mortality outcome. Further study is needed to understand the role of environmental exposure in racial disparities in health.
**Poster Abstracts**

**42-B Poster:** Genetic Susceptibility Factors for Chronic Pancreatitis in Patients of European Ancestry are Rare in African-American Patients

**Presenter:** Anna Evans Phillips, Fellow  
**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Mentors:** Dhiraj Yadav MD, MPH  
**Funding Source:** T32

**Authors:** Anna Evans Phillips MD, Jessica LaRusch PhD, Vikesh Singh PhD, Andres Gelrud MD, Nalini Guda MD, Judah Abberbock MS, Randall Brand MD, Gong Tang PhD, Thiruvengadam Muniraj MD, C. Mel Wilcox MD, Adam Slivka MD, Bimaljit Sandhu MD, Phil Greer MS, David Whitcomb MD, PhD

**Introduction:** Pathogenic variants in multiple genes contributing to chronic pancreatitis (CP) have been identified in patients of European and Asian ancestries. However, this information is lacking in CP patients of African ancestry. We evaluated the prevalence of the best-characterized susceptibility gene variants in African-American subjects in the US.

**Methods:** Prospectively enrolled patients with CP (n=232), recurrent acute pancreatitis (RAP) (n=45) and controls (n=238) in the NAPS2 studies from 2000-2014, who identified themselves as African-American were studied. Demographic, phenotypic and risk information was obtained from structured questionnaires. Genotyping for pathogenic variants in PRSS1, SPINK1, CFTR and CTRC genes was performed. Prevalence of pathogenic variants were compared in NAPS2 subjects from European and African ancestries. Principal Component Analysis (PCA) was used to investigate the role of admixture in the prevalence of pathogenic variants within the African-American cohort.

**Results:** Physician-defined alcohol etiology was present in 76.7% of CP and 33.3% of African-American RAP patients. When compared with Caucasians (n=862), the prevalence of any mutation was infrequent in African-American CP patients, overall (29 vs. 8.19%, OR 4.60 95% CI 2.74-7.74, p<0.001), and after stratification by alcohol etiology (p<0.001). Of 19 CP patients with pathogenic variants, 2 carried variants in PRSS1 (R122H and R122C), 4 in SPINK1 (all heterozygous for N34S), 12 in CFTR (2 CFTRsev, 9 CFTRBD, 1 compound heterozygote with CFTRsev and CFTRBD), and 1 CTRC (R254W) genes. Other than SPINK1 which showed a trend toward significance (p=0.059), none of the other genes showed significant difference between African-American controls and CP patients. On PCA, distribution in African-American subjects was much less homogenous than Caucasians suggesting the possibility of admixture. Moreover, the distribution in African-American subjects with and without pathogenic variants was similar suggesting that admixture is also the likely reason for inheritance of pathogenic variants in these subjects.

**Conclusion:** Pathogenic gene variants associated with CP in patients of European and Asian ancestry are uncommon in African-Americans. Those that are present appear to be due to admixture. Further studies are needed to determine genetic risk factors for pancreatitis in these subjects.
43-B Poster: Effects of unsaturated free fatty acids (uFFA) on human endothelial cells: Is there a threshold uFFA level causing cell toxicity and death in acute pancreatitis, and are uFFAs more toxic than their saturated counterparts?

Presenter: Anna Evans Phillips, Fellow
Research Interest: Translational Gastroenterology, Hepatology and Nutrition

Mentors: David Whitcomb MD, George Papachristou MD
Funding Source: T32

Authors: Anna Phillips MD, Annette Wilson PhD, Georgios Papachristou MD, David Whitcomb MD

Introduction: Hypertriglyceridemic (HTG) acute pancreatitis (AP) is often severe, with up to 30% mortality. Release of pancreatic lipase(s) into the circulation during an episode of AP facilitates massive hydrolysis of TG to free fatty acids (FFA). In addition to the pathogenic mechanism of typical AP, release of linoleic acid (LA), oleic acid (OA), Stearic Acid (SA) and other FFAs cause direct toxicity in animal models. In humans, endothelial injury results in vascular leak syndrome (VLS), linking systemic inflammation with multi-organ dysfunction. It is not known if FFA affect human microvascular endothelial cells, and if any pathologic effect is concentration-dependent. Since two pathogenic processes are possible in HTG-AP (cytokine storm and lipotoxicity), it is important distinguish the two processes. We hypothesize that Linoleic Acid (LA) and Oleic Acid cause increased cell death in human intestinal microvascular endothelial cells (HiMECs), thereby causing disruption of endothelial barrier integrity, eventually resulting in vascular leak syndrome independent of cytokines. We also hypothesize that these two uFFAs will be more toxic than their saturated counterpart, Stearic Acid.

Methods: Human intestinal microvascular endothelial cells were isolated from surgical margin specimens using CD31 marker beads. They were passaged in vitro and passages 5-15 were used for experimentation. Linoleic Acid (18:2), Oleic Acid (18:1), and Stearic Acid (18:0) were dissolved in DMSO or EtOH to create solutions of increasing concentration and applied directly to cells for 24h. Cell proliferation and cytotoxicity were tested using the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) colorimetric assay and LDH (Lactate Dehydrogenase) release assay. One-way ANOVA and post-hoc Tukey tests were used to determine significant differences.

Results: Endothelial cells treated with increasingly concentrated solutions of Linoleic Acid (18:2) have decreasing viability. Significant differences (p<0.05) in proliferation are seen between controls and concentrations of 1.25mM, 2.5mM, and 5.0mM Linoleic Acid (MTT Assay). Increased levels of LDH were released from cells with increased concentrations of Linoleic Acid. Significant differences were found between cells treated with 2.5mM Linoleic Acid, 5.0mM Linoleic Acid, and controls. When compared to one another, Oleic and Linoleic Acid – the Unsaturated fatty acids with 18 hydrocarbons - had more toxicity at HIGH dose than did Stearic Acid at high dose. All three had similar toxicity at low dose.

Conclusion: Linoleic Acid causes direct cell toxicity in human microvascular endothelial cells at concentrations at, or above 1.25 mM. Unsaturated fatty acids appear to have more toxicity at high dose compared to their saturated counterparts. Clinical studies in humans are needed to correlate the levels of specific uFFAs evidence of lipotoxicity.
**44-B Poster:** Myocardial Fibrosis is Prevalent in Smokers and Associated with Subsequent Hospitalization for Heart Failure or Death

**Presenter:** Yaron Fridman, Fellow Cardiology  
**Research Interest:** Clinical Cardiology

**Mentors:** Erik Schelbert MD  
**Funding Source:** None

**Authors:** Yaron Fridman MD, Thomas Treibel MD, Peter Kellman PhD, Timothy Wong MD, Erik Schelbert MD

**Introduction:** Smoking, an exogenous pollutant, may promote myocardial fibrosis and increase vulnerability to hospitalization for heart failure (HHF) or death. Mechanistically, myocardial fibrosis mediates susceptibility to adverse outcomes by compromising cardiomyocyte energetics through microvascular dysfunction and limiting perfusion reserve (via capillary rarefaction, perivascular fibrosis), increased afterload with systolic and diastolic dysfunction (via myocardial stiffening), and electrical dysfunction (via reentry).

**Methods:** We quantified cardiovascular magnetic resonance (CMR) measures of extracellular volume fraction (ECV) in 1,674 consecutive enrolled patients referred for CMR without amyloidosis, congenital heart disease, stress cardiomyopathy, or hypertrophic cardiomyopathy, in non-infarcted myocardium, and tracked outcomes prospectively.

**Results:** Smokers (n=233) had higher median ECV than non-smokers (n=1,441): 29.8% (IQR: 26.8–32.3) vs. 27.4% (IQR: 25.2–30.2) (p<0.001). Nearly 50% of smokers exhibit high levels of myocardial fibrosis (ECV>30) (n=115/233). Smoking remained associated with higher ECV in linear regression models adjusting for a total of 15 variables capturing demographic, comorbidity, and medication differences (p<0.001). (Age, gender, race, smoking status, diabetes, hypertension, renal function, ejection fraction, left ventricular mass indexed, myocardial infarction, ACE or ARB use, Beta-blocker use, statin use.) Over a median of 2.6 years (IQR: 1.4–3.7), 54 smokers had 17 incident hospitalizations for heart failure and 43 deaths. In smokers, ECV was associated with events in multivariable Cox regression models adjusting for age, gender, myocardial infarction, ejection fraction, renal function, and history of CABG; HR: 1.55 (95% CI: 1.15–2.08 per 5% increase in ECV) (p=0.004).

**Conclusion:** Smoking may promote myocardial fibrosis even after adjusting for many potential confounders. In smokers, myocardial fibrosis and associated with hospitalization for heart failure or death. These data further emphasize the potential for environmental pollutants to disrupt myocardial architecture and confer vulnerability to adverse outcomes.
**Introduction:** Patients referred for overnight polysomnography have an increased prevalence of atrial fibrillation (AF). Obstructive sleep apnea (OSA) is associated with AF, and emerging data suggest self-reported short or long sleep duration may predict incident AF risk as well. Objective data linking sleep duration and AF are lacking.

**Methods:** Consecutive, digitally available, diagnostic sleep studies from March 1999 to December 2015 performed in University of Pittsburgh Medical Center sleep labs at Montefiore, Monroeville, Mercy, Shadyside, and McKeesport Hospitals were examined. Patient demographics, sleep duration, apnea-hypopnea index (AHI), and predominant cardiac rhythm were extracted from the interpreting physicians’ reports. Patients in AF at the time of the study were compared to those in sinus rhythm. Population characteristics were compared using Wilcoxon signed-rank and chi-squared tests.

**Results:** A total of 23,421 adults underwent diagnostic overnight polysomnography during the study period and were available for analysis. Of these, 22,612 were in predominant sinus rhythm and 78 were in atrial fibrillation at the time of study. Patients with predominately paced rhythms and those without physician comment on cardiac rhythm were excluded, leaving 22,690 for analysis. There was no difference between the participants with AF compared to those without AF with respect to body mass index (median 31.7 vs 32.7 kg/m2, \( P=0.47 \)) or sex (57.7 vs 50.2% male, \( P=0.23 \)). Patients with AF were older (67.0 vs. 50.4 years, \( P<0.001 \)) and had greater OSA severity as assessed by the apnea hypopnea index (20.9 vs. 10.3 events/hr, \( P=0.001 \)). Sleep duration was disproportionately shorter in those with AF with a difference in median total sleep time of 67 minutes (238 vs 305 min, \( P<0.001 \)).

**Conclusion:** In a real-world cohort of consecutive patients who received diagnostic overnight polysomnography within one hospital system, patients in atrial fibrillation at the time of sleep study are more likely to have shorter sleep duration. Sleep duration in this study was measured objectively in the controlled setting of the sleep lab, adding to findings from prior studies relying on self-report. However, given that OSA was the primary indication for polysomnography, the generalizability of these findings to patients without OSA is unclear. Further analysis is required to identify the stages of sleep that differ by cardiac rhythm and whether objectively assessed short sleep is a predictor for subsequent development of AF on longitudinal follow-up.
Introduction: Early evidence suggests that slowing of gait speed while performing cognitive tasks while walking, also referred to as dual-tasking, is related to brain amyloid deposition in cognitively normal mobility unimpaired older adults. Working memory is an executive function task integral to routine functioning. Working memory tasks performed while walking under dual-task conditions may influence gait parameters in relation to cognitive demands of the underlying task, and amyloid deposition may further influence this relationship. We assessed the influence of amyloid positivity on dual-task interference on gait induced by three working memory tasks of varying cognitive demands in cognitively normal mobility unimpaired older adults.

Methods: Brain amyloid burden was determined using the Pittsburgh B (PiB) ligand on PET. Overall amyloid burden was dichotomized as high-amyloid (PiB+) and low-amyloid (PiB-) state based on standardized uptake value ratios (SUVR) referenced to the cerebellum on global six cortical regions using a SUVR of 1.4 as cutoff. Performance on n-back verbal working memory paradigms of increasing difficulty (0-back, 1-back and 2-back tasks) was measured using computerized paradigms while standing. Gait speed was measured on the GaitMat II on regular walking condition and while performing the n-back verbal working memory paradigms (0-back, 1-back and 2-back tasks). Order of tasks was randomized between subjects using a computer generated paradigm. Repeated measures analysis of variance was used to compare the two groups across four walking conditions (regular walk without dual tasking, and 0-back, 1back and 2 back dual-task walking conditions) adjusted for age.

Results: The two groups (16 PiB+, 8 PiB-) were comparable in age (76 years), education, general cognitive and physical performance status, processing speed, grip strength, and single-task gait speed (1.14 vs 1.16 m/sec, p=0.2). Gait speed was slower with increasing working memory dual-task difficulty (1-back and 2-back > 0-back task) with PiB+ subjects showing significantly greater declines in gait speed across working memory difficulty (between-subjects effects: F=4.95, p=0.037).

Conclusion: Amyloid positivity in cognitively normal mobility impaired older adults influences the magnitude of gait slowing associated with increasing working memory load under dual-task conditions.
48-B Poster: Facility- and Home-Based Cardiac Rehabilitation Achieve Similar Magnitude of Functional Improvements

Presenter: Garrett Kellar, Graduate Student Geriatric Medicine

Research Interest: Clinical

Mentors: Daniel Forman MD

Funding Source: Clinical Program Project Funding

Authors: Garrett Kellar MS, Nicholas Bello BS, Andrew Althouse PhD, Kelly Allsup MS, Nicole Lemieux MD, James Kostra MS, Thomas Byard MS, Rebecca Smith MS, Juliet Mancino MS, Jessica Shultz MS, Karen Tarolli MSN, ACNP-BC, Gavin Hickey MD, Ross Arena PhD, Daniel Forman MD

Introduction: Cardiac rehabilitation (CR) has been demonstrated to increase functional capacity in patients with cardiovascular disease (CVD). However, research has found only 14 to 31% of eligible patients participate in facility-based (FB) CR; participation appears to be even lower within the Veteran Administration (VA) with only 8 to 10% of eligible Veterans participating. Home-based (HB) CR may be a viable alternative to expand CR utilization. In a VHS quality improvement project, we compared functional gains achieved in FB-CR versus HB-CR for Veterans with CVD.

Methods: Veterans diagnosed with CVD were assessed pre- and post- CR including medical and functional assessment [6 Minute Walk Distance (6MWD), Gait Speed (GS) and Timed Up and Go (TUG)]. Low risk patients were given the option to participate in the FB- or HB-CR program. Moderate and high risk patients participated only in FB-CR. FB-CR entailed standardized exercise training and education; 1 to 3 hospital-based sessions per week over 12 weeks (range of 24-36 sessions). HB-CR entailed an initial onsite exercise education session and then verbal exercise review/reinforcement and education over the phone, one session per week for 12 weeks. After 12 weeks, patients in both groups were reassessed.

Results: There were significant improvements in 6MWD for both HB (PRE 362 ± 70 versus POST 408 ± 74; p=.018) and FB (PRE 296 ± 103 versus POST 337 ± 88; p=.023). The magnitude of change was comparable for HB versus FB (46 ± 73 versus 41 ± 75) with no significant difference (p= 0.944). Comparable results with no significant difference between groups were seen in GS (p= 0.239) and TUG (p= 0.224).

Conclusion: FB- and HB-CR were associated with similar improvements in key functional metrics, suggesting that both programs achieve valuable functional gains in patients that ranged in CV disease severity. This extends the promise of HB-CR as a format of CR that not only has the potential to increase participation, especially for the many eligible patients who are curtailed by logistics, but to achieve similar efficacy. Functional recovery after a cardiovascular event is a critical step towards improved quality of life and reduced disability.
**50-B Poster:** Hypoglycemic Episodes in ICU patients on glucose containing Prismasate CRRT compared to non-glucose containing Phoxillum CRRT

**Presenter:** Melbeth Lusica, Fellow  
**Research Interest:** Clinical Renal-Electrolyte  
**Mentors:** None  
**Funding Source:** None  
**Authors:** Melbeth Lusica MD, Badamkhand Baatarkhuu MD

**Introduction:** More than a decade ago, hyperglycemia has been recognized as a risk factor for adverse outcomes in critically ill patients. During a landmark study using intensive insulin therapy in the medical ICU, it was noted that 3.1% to 18.7% of patients experienced a glucose value <40 mg/dl. It was found that in the ICU, severe hypoglycemia (<40 mg/dl) is an independent risk factor for death. There is a clear association between severity of ICU patients and the occurrence of hypoglycemia. Even a single episode of severe hypoglycemia conferred an increased risk of mortality. The mechanism leading to increased mortality still has not been elucidated. CVVH treatment is one of the risk factors associated with occurrence of hypoglycemia in the ICU. Phosphate-containing dialysates such as Phoxillum, protect against hypophosphatemia but do not contain any glucose, thus, may have potential for contributing to hypoglycemic events in the ICU compared to glucose containing dialysate Prismasate.

**OBJECTIVES:** In this Quality Improvement Project, we evaluated the true incidence of hypoglycemia in patients on CRRT using glucose containing dialysate, Prismasate versus non-glucose containing dialysate Phoxillum. We also examined presence of risk factors for severe hypoglycemia in ICU patients on continuous renal replacement therapy and its association with mortality.

**Methods:** All episodes of severe hypoglycemia (glucose value <40 mg/dl) while on CRRT were identified in all adult intensive care units (medical, surgical, cardiac, and transplant ICUs) of university medical center in two time periods, each were of 3 months duration. First is between 10/1/15 to 12/31/15 when Prismasate was sole dialysate available for use. Second time period is between 4/1/15 to 6/30/16 when both Prismasate and Phoxillum dialysates were available for use. Each hypoglycemic reading < 40 mg/dl is considered an individual event. Incidence of severe hypoglycemia is computed for both Prismasate and Phoxillum groups. Risk factors previously associated with severe hypoglycemia in the ICU setting were identified around the moment of hypoglycemia. Incidence of death was ascertained for each patient who presented with severe hypoglycemia during the time periods studied. Data was collected from electronic medical records.

**Results:** Pending

**Conclusion:** Pending
51-B Poster: Outcomes of Heart Failure Admissions under Observation versus Short Inpatient Stay

Presenter: Ahmad Masri, Fellow Cardiology
Research Interest: Clinical
Mentors: Suresh Mulukutla MD
Funding Source: None
Authors: Ahmad Masri MD, Andrew Althouse MD, Jeffrey Mckibben BS, Floyd Thoma BS, Michael Mathier MD, Ravi Ramani MD, Jeffrey Teuteberg MD, Oscar Marroquin MD, Joon Lee MD, Suresh Mulukutla MD

Introduction: Heart failure is the leading cause of admission for patients over the age of 65. Based on the current practice model, patients get admitted either under observation or inpatient stays; however, there is little data on whether this designation reflects the clinical status of a patient. Given the logistical and financial implications, we sought to understand the outcomes of patients admitted under observation versus inpatient status who remained in-hospital for fewer than 2 days

Methods: From 2008 through 2015, our multi-site health system saw 21,339 unique patients totaling 52,493 hospital admissions with a primary diagnosis of HF. Patients were excluded if they underwent cardiac surgery (n=611), heart transplant (n=187), LVAD insertion (n=198), or if they died during hospitalization (n=1839). Of the remaining 50,654 discharges, two groups were identified; admitted under inpatient status but discharged within 2 days (INPT group) and admitted under observation (OBS group). The primary outcomes were heart failure readmission, all-cause readmission and all-cause mortality within 1 year of discharge. Outcomes are presented using Kaplan-Meier estimates. Hazard ratios for patients admitted under inpatient status vs. observation status were computed using the Andersen-Gill method in the Cox proportional-hazards model

Results: 8,709 admissions (17%) under inpatient status resulted in discharge within 2 days of admission; 2,648 admissions (5%) were designated under observation. HF readmission rate at 1 year was 55.3% in INPT vs 66.5% in OBS; HR 0.75 (95% CI 0.71-0.80), p<0.01. All-cause readmission rate at 1 year was 70.7% in INPT vs 82.5% in OBS; HR 0.74 (95% CI 0.70-0.78), p<0.01. All-cause mortality at 1 year occurred in 25.2% of INPT vs 24.2% of OBS; HR 1.03 (95% CI 0.95-1.12), p=0.46.

Conclusion: Patients admitted with inpatient status who are discharged within 2 days had lower readmission rates and equivalent mortality to patients admitted for observation.
**52-B Poster:** Persistent Pulmonary Hypertension following Transcatheter Aortic Valve Replacement Is Common and Associated with Higher Mortality

**Presenter:** Ahmad Masri, Fellow Cardiology

**Research Interest:** Clinical Cardiology

**Mentors:** Joao Cavalcante MD

**Funding Source:** None

**Authors:** Ahmad Masri MD, Islam Abdelkarim MD, Michael Sharbaugh MPH, Andrew Althouse PhD, Jeffrey Xu BS, Stephen Chan MD, William Katz MD, Frederick Crock MD, Mathew Harinstein MD, Dustin Kliner MD, Forozan Navid MD, Joon Lee MD, Thomas Gleason MD, John Schindler MD

**Introduction:** Pulmonary hypertension (PH) is highly prevalent in patients with severe aortic stenosis (AS) referred for transcatheter aortic valve replacement (TAVR) evaluation. We sought to assess the prevalence and factors associated with residual PH following TAVR and its relationship with mortality.

**Methods:** A single-center observational study was performed, including 458 patients who underwent TAVR from July 2011 through January 2016. We investigated the prevalence of moderate or greater PH (PA systolic pressure > 45 mmHg on echocardiography) prior to TAVR, the prevalence and predictors of residual PH (PA systolic pressure > 45 mmHg on post TAVR follow up; median 29 days (IQR 29-36 days). Logistic regression was used to identify baseline factors associated with increased risk of residual PH; Kaplan-Meier curves and Cox models were used to quantify the effect of residual PH on subsequent mortality.

**Results:** Of the 458 TAVR patients, 165 (36%) had = moderate PH on echo prior to TAVR. Of these, 91 (20%) had residual = moderate PH on post-TAVR echo. Mortality at 2 years in patients with no baseline PH, patients with baseline PH that improved, and patients with residual moderate to severe PH were 16%, 23%, and 35%, respectively (p=0.035). After adjusting for STS PROM and TAPSE, this relationship persisted with a HR of 2.35 (95% CI 1.15, 4.79, p=0.019). Prior moderate to severe TR (OR 3.05, 95% CI 1.50, 6.18, p=0.002) and LVEF<50% (OR 2.31, 95% CI 1.19, 4.47, p=0.013) were associated with residual PH.

**Conclusion:** Persistent moderate or greater PH at one month post TAVR is common and strongly associated with higher 2 year mortality as compared to patients with resolved PH. Pre-procedural moderate to severe TR and LVEF<50% are predictors of residual PH and subsequent mortality. Whether residual PH could be a modifiable target for future therapies beyond TAVR requires further investigation.
**53-B Poster:** Tc-99m PYP Scan for Cardiac Amyloidosis: Will a Single Image at 1 hour Suffice?

**Presenter:** Ahmad Masri, Fellow  
**Research Interest:** Clinical Cardiology

**Mentors:** Prem Soman MD  
**Funding Source:** None

**Authors:** Ahmad Masri MD, Ricardo Nieves MD, William Follansbee MD, Joao Cavalcante MD, Prem Soman MD

**Introduction:** Tc-99m PYP has high diagnostic accuracy for cardiac ATTR amyloidosis. Imaging protocols have variably used 1-hr and 3-hr imaging time points. We sought to determine if a single set of images at 1hr could make the diagnosis with equal accuracy and improved efficiency.

**Methods:** Patients with suspected ATTR CA were prospectively evaluated with Tc-PYP scintigraphy, using 25 mCi of tracer, and a pre-defined multi-point protocol (1 and 3 hr planar and SPECT imaging) when possible. Visual semi-quantitative (grades 1-3, =2 defines a positive test) and quantitative heart to contralateral lung ratio (H/CL = 1.5 defines a positive test) scales were utilized. SPECT imaging was used to confirm the myocardial (vs blood pool) location of tracer activity when the planar images were equivocal.

**Results:** Among 104 patients studied, 36 (35%) had a positive PYP scan. Complete 1hr and 3 hr data were available in 100 patients (96%). In patients with a positive scan, the mean H/CL ratio at 1 and 3 hr were 2±0.3 and 1.8±0.3, respectively. The mean visual semi-quantitative scores at 1 and 3 hr were 2.9±0.6 and 2.6±0.8, respectively. All patients with 3h positive scan were also positive at 1 hr; 4 (11%) patients had positive scans at 1 hr that turned negative at 3 hr by either semi-quantitative or H/CL ratio assessment. No scan that was negative at 1 hr turned positive at 3 hr. Two (5%) patients had higher H/C ratio on the 3 hr scan as compared to 1 hr scan, but without affecting the test interpretation.

**Conclusion:** An efficient Tc-99m PYP protocol with a single-time point imaging at 1 hr has similar accuracy to imaging at 3 hr.
Red meat allergy: an unrecognized cause of anaphylaxis in western Pennsylvania

Presenter: Shaylar Padgett, Fellow
Research Interest: Clinical Pulmonary, Allergy and Critical Care Medicine

Mentors: Merritt Fajt MD
Funding Source: None

Authors: Shaylar Padgett MD, Andrej Petrov MD, Merritt Fajt MD

Introduction: Galactose-alpha-1,3-galactose (alpha-gal) is a carbohydrate epitope found in mammalian red meats. A delayed IgE-mediated allergic reaction to red meats has been described and is known as alpha-gal allergy. Alpha-gal allergy is a rare but an increasingly prevalent food allergy most commonly diagnosed in the southeastern region of the United States. Sensitization is through a tick bite from the Amblyomma americanum (Lone Star tick) whose major host is the white-tailed deer. The purpose of this study is to increase awareness of alpha-gal allergy in western PA as well as to guide diagnosis and management.

Methods: We present a patient seen in a university Allergy Immunology clinic with prior history of several episodes of anaphylaxis and emergency department visits following red meat ingestion. The patient was tested with a serum alpha-gal specific IgE level, serum IgE levels to red meats, total serum IgE level, immediate hypersensitivity skin prick testing to commercial meat extracts and fresh meats to evaluate for alpha-gal allergy.

Results: Serum alpha-gal specific IgE level was positive at 18.9 kU/L (normal value <0.35kU/L). Total serum IgE level was elevated at 449 IU/mL. Serum IgE levels for beef and pork were undetectable. Skin prick testing was positive to commercial extracts of beef and pork. Prick to prick skin testing with fresh pork, lamb and beef were profoundly positive [wheal x flare in mm: 8x23, 16x36 with pseudopods, 20 x35, respectively]. These tests confirm the diagnosis of alpha-gal allergy in this patient and he was advised to avoid beef, pork and lamb in his diet.

Conclusion: This case confirms that alpha-gal allergy is present in western PA. History of delayed anaphylaxis following red meat ingestion should prompt an allergy evaluation. Clinical history along with positive serum alpha-gal specific IgE and skin prick testing to fresh meats was essential in this diagnosis and subsequent management in our patient.
**57-B Poster:** Epidemiology and Risk Factors of Respiratory Invasive Fungal Infections (IFI) and Fungal Colonization (COL) Complicating Influenza (flu) Among Solid Organ Transplant (SOT) Recipients

**Presenter:** Mana Rao, Fellow

**Research Interest:** Clinical Infectious Diseases

**Mentors:** M Hong Nguyen MD

**Funding Source:** None

**Authors:** Mana Rao MD, Cornelius J Clancy MD, M Hong Nguyen MD

**Introduction:** Lung IFIs are increasingly reported after flu. IFIs are also common following SOT. The rate of IFI complicating flu in SOT recipients is unknown.

**Methods:** Retrospective review of consecutive patients (pts) transplanted from Jan 1, 2008-Dec 31, 2014. Pts who died within 100 days of SOT were excluded. Flu-associated IFI was defined according to revised EORTC/MSG criteria if IFI occurred within 100 days of flu. COL was defined as recovery of mold from airways in absence of IFI.

**Results:** 2,717 pts were included (1163 kidney +/- pancreas (Ki), 708 lung (Lu), 529 liver (Li), 247 heart (Ht) and 70 small bowel/multivisceral (SB) transplant. 64 cases of flu were identified, most commonly among SB (5.7%) and Lu (5%), followed by Ki, Ht and Li (1.5%, 1.2% and 0.8%, respectively). Median time from SOT to flu was 27.8 months (1.2 mos-6 years). 86% were community-acquired. 80% and 20% were caused by Influenza A and B, respectively. Only 1 pt had renal failure requiring dialysis. 71% required admission, and 11% intubation. 26% had abnormal radiograph (CXR): 3 with typical findings of viral pneumonia (PNA), 14 with consolidation. Causes of bacterial PNA were identified in 9% (6); S. aureus was most common (4). Molds were recovered from 22% (14) of pts. Pathogenic molds (14%) included Aspergillus spp (8, 2 of which co-existed with Rhizopus spp) and Scedosporium. Non-pathogenic molds included Penicillium (4, 1 with Paecilomyces) and sterile mycelia (1). 64% (9/14) of pts with + mold cultures were on an antifungal at the time of flu. 50% (7/14) of + cultures were present at time of flu diagnosis; the remainder were + at a median of 60 days after flu. 1 patient (Ki) had IFI (A. niger; 2%), and survived with azole treatment; the other 13 (20%) were COL. Univariate analysis identified Lu transplant (p=0.007) and recent immune augmentation as associated with post-flu COL or IFI (p=0.03). 57% of pts with COL or IFI were hospitalized for flu vs 86% of patients without + culture (p=0.03). Need for intubation, type of Influenza virus (A or B), and consolidation on CXR were not associated with COL or IFI.

**Conclusion:** Overall, the rate of post-flu IFI was only 2%. Flu affected 5% of Lu transplant pts, and 22% of these pts had mold COL. COL was rare outside of Lu transplant. It is unclear whether mold COL or IFI is increased after flu since up to 40% of Lu transplant pts are reported to be COL. Routine antifungal prophylaxis (px) is not recommended for all SOT pts with flu. The value of px at time of flu for SOT pts with recent immune augmentation or Lu recipients with concurrent COL should be studied.
Poster: Post operative complications and SSI after spine and orthopedic surgeries: 5 year review

Presenter: Mana Rao, Fellow
Research Interest: Clinical Infectious Diseases

Mentors: Mohamed Yassin MD, Karin Byers MD
Funding Source: None

Authors: Mana Rao MD, Mahir Khan MPH, Tammi Minnier, RN, MSN, Christine Bridge MBA, Heather Dixon RN, MSN, Karin Byers MD, Mohamed Yassin MD

Introduction: Non emergent orthopedic and spine surgeries aim at improving quality of life of patients. SSI is a major surgical complication. Favorable outcome requires coordinated efforts to prevent SSI and many other non infectious complications. This study aims at describing surgical complications and identify opportunities for quality improvement.

Methods: This is a single academic medical center retrospective review of cases of spinal fusion, laminectomy, knee and hip prostheses. Patients’ demographics, BMI, smoking, MRSA screen and comorbidity index were collected. Surgical duration, antibiotic prophylaxis, anesthesia class, length of stay and mortality risk were recorded. Finally, complications including 90 day readmission, HAIs, venous thromboembolism and other reports to risk master.

Results: There were total of 6376 surgeries between July 1st, 2011 till end of June 2016. The mean age was 59.2 years (SD 14.4), mean Length of stay was 4 days (SD 4.2). There were 113 HAIs reported to the NSHN with 58 SSI (0.9%) with Staph aureus as the most common cause in 32 (55.2%) cases. MRSA screen was only done in 347 cases and MRSA was detected in only 10 patients. There were 367 (5.8%) readmissions. There were 1002 risk master reports with 437 (6.9%) class C, D and E reports.

Conclusion: Surgical-related complications are largely preventable and need to be evaluated prospectively to improve surgical safety. Significant number of infections in surgical patients are not SSI. MRSA screen was performed much less than what was recommended and positive results were much less frequent than what was expected.
**Poster Abstracts**

**59-B Poster:** Improving Adherence To The ACC/AHA Cholesterol Guidelines In a Tertiary Care Center Subspecialty Endocrine Practice

**Presenter:** Karen Selk, Fellow
**Endocrinology and Metabolism**

**Research Interest:** Clinical

**Mentors:** Erin Kershaw MD

**Funding Source:** None

**Authors:** Karen Selk DO, Adasia Ritenour, Erin Kershaw MD

**Introduction:** Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality among the diabetic population. Statin use has been found to be beneficial for both primary and secondary prevention of ASCVD. In November 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) released updated guidelines for the treatment of hyperlipidemia to reduce atherosclerotic cardiovascular risk. The guidelines identify high-risk patients who would benefit the most from statin therapy including patients 40-75 years old with diabetes mellitus and LDL-C 70-189 mg/dL, and others with a 10-year ASCVD risk =7.5%. The guidelines recommend all patients with diabetes aged 40-75 years be treated with a moderate intensity statin. Use of the ASCVD risk calculator can be used in this population as it can help identify patients without known clinical ASCVD who would benefit from statin intensification. The goals of this study were to assess statin prescribing patterns, improve adherence of diabetic patients to the ACC/AHA cholesterol guidelines, and improve compliance with statin therapy in patients with an ASCVD risk of =7.5%. To achieve these goals, we assessed physician knowledge and practices as well as adherence of diabetic patients to the ACC/AHA cholesterol guidelines before and after an intervention designed to improve adherence to the ACC/AHA cholesterol guidelines.

**Methods:** Physician knowledge and practice were assessed using a survey of ten questions including two clinical vignettes, use of the ASCVD calculator, and how statin intolerance was addressed and documented. A YouTube presentation outlining recommendations for this population and data on statin prescription in 2016 was viewed. Quarterly reports identified diabetic patients from January 2016 through June 2016. Individual patient charts were reviewed for documentation and prescription of the appropriate statin documented 10-year ASCVD risk, and documentation of statin intolerance. ASCVD scores were calculated for each patient. These results will then be compared to 2017 data.

**Results:** Sixty-four percent of diabetics were on a moderate or high intensity statin with 27% not on a statin. Sixty-eight percent of type II diabetics were on moderate/high intensity statin therapy in comparison to 52% of patients with type I diabetes. Type I diabetics were also less likely than type II diabetics to be on any statin (32% vs 25%). The ASCVD 10 year risk was documented in less than 5% of encounters.

**Conclusion:**
**Introduction:** The Arctic Front Cryoballoon System is a technology in which substrate alterations in patients with atrial fibrillation (AF) recurrence have not been well characterized. In this study, we evaluated sites of pulmonary vein (PV) reconnections and the accuracy of the Achieve circular mapping catheter in detecting these reconnections after cryoablation.

**Methods:** This study included 15 patients undergoing redo AF ablation after a prior single cryoablation procedure. PV reconnection sites were determined by measuring PV signals and high output pacing from 4 vectors of the Achieve catheter. The results were compared with a roving mapping catheter guided by rotational intracardiac echocardiography (ICE) in the left atrium.

**Results:** All patients had PV reconnections (2.1 +/- 0.8 veins/patient). The left superior PV was most commonly reconnected (n=11), whereas the right inferior PV was least likely (n=3). Both carinas (left: n=11; right: n=7) and left atrial appendage ridge (n=11) were also frequently reconnected. Mapping with the Achieve catheter showed a PPV 97% and NPV 92% when compared with ICE guided mapping. In 2 patients, right superior PV reconnection was not identified by the Achieve.

**Conclusion:** During redo AF ablation after index cryoablation, multiple PVs are usually reconnected, with both carinas and left atrial appendage ridge being common sites of reconnection. The Achieve mapping catheter was able to identify reconnection with high positive and negative predictive values.
**61-B Poster:** Association of Intradialytic Hypertension with Left Ventricular Mass in Hemodialysis Patients enrolled in the Blood Pressure in Dialysis (BID) pilot study.

**Presenter:** Amith Shamir MD, Fellow Renal-Electrolyte

**Research Interest:** Clinical Renal-Electrolyte

**Mentors:** Manisha Jhamb MD

**Funding Source:** None

**Authors:** Amith Shamir MD, Ameet Karambelkar MD, Yi Yao MS, Jonathan Yabes PhD, Manisha Jhamb MD

**Introduction:** Although the majority of patients on hemodialysis (HD) experience a decline in systolic blood pressure (SBP) during HD, 15-20% of the patients experience an increase in SBP during HD. This apparent paradoxical phenomenon is known as intradialytic hypertension (IDH), and has been associated with increased morbidity and mortality. However, the underlying mechanisms are not fully understood. We aim to evaluate the association between intradialytic change in SBP and left ventricular (LV) mass at baseline in HD patients enrolled in the BID study.

**Methods:** We conducted a cross sectional analysis of hypertensive HD patients enrolled in the BID study and calculated the average difference of SBP pre and post HD for each participant for all HD sessions for a month. Patients were categorized into three groups according to the difference: Group 1: >10mm Hg increase in SBP (IDH); Group 2: >10mm Hg decrease in SBP; and Group 3: increase or decrease in SBP = 10mm Hg. The three groups were compared using means and standard deviations (SD) (or median and interquartile range) for continuous variables; and frequencies and percentages for categorical variables. LV mass was measured using cardiac MRI and compared within the 3 groups and was adjusted for variables using multivariable regression models.

**Results:** Among the 83 participants, 6 (8%) had IDH. Patients with IDH (Group 1) had a significantly greater LV mass as compared to other 2 groups: 201g ± 55.3, 141g ± 40, 155g ± 47.8 in Group 1, 2 and 3 respectively, p=0.007). This association remained significant even after adjusting for age, sex, intradialytic weight gain, diabetes, dialysis adequacy, RAAS inhibitor use (P <0.001). There was no significant association between IDH and any of the demographic, clinical and laboratory variables examined including age, race, dialysis vintage, estimated dry weight, dialysis adequacy, hemoglobin, albumin and history of diabetes or coronary artery disease except for serum calcium.

**Conclusion:** Hypertensive HD patients with IDH have greater LV mass, which may contribute to their increased morbidity and mortality.
**62-B Poster:** Hereditary Pancreatitis in the United States: Clinical Characteristics, Survival and Rates of Pancreatic Cancer

**Presenter:** Celeste Shelton, Graduate Student  
**Research Interest:** Clinical Gastroenterology, Hepatology and Nutrition

**Mentors:** David Whitcomb MD, PhD  
**Funding Source:** T32

**Authors:** Celeste Shelton MS, Chandraprakash Umapathy MD, MS, Dhiraj Yadav MD, MPH, David Whitcomb MD, PhD

**Introduction:** Hereditary pancreatitis (HP) is a highly penetrant autosomal dominant disease typically caused by mutations in PRSS1, but with a broad range of clinical characteristics. Accurately describing the clinical symptoms and outcomes such as pancreatic cancer is critical to understanding risk and modifying factors.

**Methods:** HP probands and their family members were prospectively recruited into an IRB-approved HP study. Subjects completed medical and family history questionnaires, and were asked to provide medical records. DNA was tested for core pathogenic PRSS1 mutations. Overall survival or development of pancreatic cancer until Dec 31, 2015 was determined using the Social Security and National Death Index datasets.

**Results:** 183 symptomatic PRSS1 carriers and 37 silent PRSS1 carriers from 69 families were identified. With the identification of an additional 12 individuals from 6 families meeting clinical criteria for HP without a core PRSS1 mutation, PRSS1 mutations were detected in 94% of these symptomatic subjects. Cumulative risk for pancreatitis in PRSS1 carriers was 75.1% (95% CI 68.4-80.3) at 25 years and 85.9% (95% CI 79.7-90.2) at 50 years. Cumulative risk for diabetes mellitus was 28.9% (95% CI 17.2 - 38.9) at 50 years in symptomatic PRSS1 carriers. The most frequently detected PRSS1 mutations were R122H (84.1%) and N29I (11.5%). A significant difference was identified in the reported age at first diagnosis with pancreatitis between individuals with and without an identified mutation (median 7 years and 20.5 years, respectively). Hereditary pancreatitis was diagnosed at a median age of 13.5 years in PRSS1 carriers. A total of 29 symptomatic PRSS1 carriers were identified as deceased. Median overall survival for symptomatic PRSS1 carriers was 79.3 years (CI 95% 75.1-85.7). Only 3 symptomatic carriers developed pancreatic cancer according to NDI records.

**Conclusion:** Patients from HP families display significant variability in age of onset, severity, and risk for complications, including development of pancreatic cancer. The incidence of pancreatic cancer in this prospectively ascertained cohort was much lower than anticipated. The variability in clinical symptoms and outcomes suggest that additional genetic, environmental or other susceptibility and modifying factors play a significant role in the clinical course of HP.
**63-B Poster:** Evaluation of Valganciclovir Dosing in Renal Transplant Recipients using Normalized and Absolute Glomerular Filtration Rate

**Presenter:** Rohan Singh Paul, Fellow  
Renal-Electrolyte

**Research Interest:** Clinical  
Renal-Electrolyte

**Mentors:** None

**Funding Source:** Fellowship Program

**Authors:** Rohan Paul MBBS, Sundaram Hariharan MBBS, Chethan Puttarajappa MBBS

**Introduction:** Clinicians generally use the MDRD or CKD-EPI derived equations to gauge renal function, which typically normalize glomerular filtration rate to a body surface area of 1.73 m². However for drug dosing, it is recommended that absolute renal function is measured and used. The authors hypothesized that since most clinicians do not use absolute GFR, that valganciclovir is being dosed inappropriately in certain individuals which may predispose to leukopenia.

**Methods:** This retrospective study included 225 renal transplant recipients from UPMC who were transplanted between January 1st, 2013 and December 31st, 2015. Adult recipients with either living or deceased donors, both genders and all racial and ethnic groups were included for the study. MDRD reported GFR was converted into absolute GFR by multiplying by an individual’s BSA divided by 1.73. The delta-GFR and percentage change over the MDRD value was calculated. Patients were categorized into three BSA tertiles and the appropriateness of valganciclovir dose among these three groups at three months post-transplant was determined by comparing the recommended dose versus the dose that was actually prescribed. The point prevalence of leukopenia (Leukocyte count < 3500) among the three groups was determined.

**Results:** Median BSA was 1.89 m² (IQR: 1.74 – 2.09). The percentage of patients with the following changes in GFR were 0-5 ml/min: 47.1%, 6-10 ml/min: 30.2%, 11-20 ml/min: 20.0%, > 20 ml/min: 2.7%. There was a statistically significant difference in valganciclovir dosing among the three BSA categories (p < 0.001). The percentage of patients overdosed with valganciclovir was 46% in the lowest BSA tertile versus 20% in the middle BSA tertile. The percentage of patients underdosed was 33% in the highest BSA tertile versus 24% in the middle BSA tertile. There was no difference in the point prevalence of leukopenia across the BSA groups (p = 0.819).

**Conclusion:** This study demonstrates more inappropriate valganciclovir dosing in renal transplant recipients with lower and higher BSAs. Interestingly it did not translate into a higher rate of leukopenia suggesting that valganciclovir overdosage is probably safe and aligns with current recommendations to search for alternative explanations for leukopenia as opposed to implicating a valganciclovir dose effect (Kotton et al, 2013). Conversely, the study also showed relative underdosing in patients with higher BSAs. In view of the known risk of breakthrough CMV infection from inadequate prophylaxis (Stevens et al, 2015), the authors recommend that absolute GFR be utilized for valganciclovir dosing particularly in patients with higher BSAs.
**Introduction:** Diabetes self-management education (DSME) participation is abysmal despite known benefit. Reported barriers include confusion regarding referral criteria and limited access.

**Methods:** The purpose of this study was to examine DSME referrals and clinical profiles of patients with T2DM, ages 18-75, after dissemination of an evidence-based referral algorithm and one month after integrating DSME services in two rural primary care (PC) practices. Provider reactions to the algorithm were assessed through focus groups. A retrospective chart review was conducted to collect A1c, risk factors, comorbidities and referrals at one month.

**Results:** Providers reported that the algorithm is appropriate, but too complicated for practical application. They agreed that high A1c and new diagnosis warrant referral, but were not in uniform agreement on additional criteria. Over half of the 270 patients who presented during the study period were at goal A1c (<7%); however, most had three risk factors and >1 comorbidity (table). Of the 4% of patients referred to DSME, most had A1c >8%. Findings indicate that using A1c criteria alone for referral may overlook at-risk patients who can benefit from DSME. In addition, referrals remained low among poorly controlled patients despite dissemination of guidelines and improved DSME access.

**Conclusion:** Although brief, the study suggests ongoing promotion of the algorithm with attention to risk factors and comorbidities may be needed to improve referrals.
**65-B Poster:** Revisiting Antibiotic Stewardship in Long term Care Residents

**Presenter:** Keisha Ward, Fellow  
Geriatric Medicine

**Research Interest:** Clinical

**Mentors:** John Naumovski MD  

**Funding Source:** None

**Authors:** Keisha Ward MD, Christina Bungo DO, John Naumovski MD, David Nace MD

**Introduction:** In the United States, approximately 1.4 million people live in more than 15,000 long term care (LTC) facilities. Urinary tract infection (UTI) is still the most frequent indication for antibiotic use in LTC facilities. An estimated 25 to 75 % of antibiotic prescriptions for LTC residents do not meet clinical guidelines for appropriate prescribing, which is troubling. The aim of this study is to evaluate antibiotic use and prescribing habits from December 2015 to July 2016 at Charles Morris Nursing and Rehabilitation Center in Pittsburgh, Pennsylvania. Loeb’s minimum criteria for initiation of antibiotics was used in LTC residents with goals of improving testing and antibiotic stewardship thereby reducing unwarranted antibiotic use.

**Methods:** Patient demographic data, symptoms, urinalyses and urine cultures, and antibiotic use were collected in LTC residents who met criteria for the treatment of UTI.

**Results:** The study included a total of 76 residents of which 60% were female. The average age was 86 years. The most common symptom reported was confusion. Urine cultures were sent in 95% of cases; 40% were positive for Escherichia coli (>100,000 colony forming units). Of the total number of residents, 10% were appropriately prescribed antibiotics as per Loeb’s criteria.

**Conclusion:** The results suggest that there was a significant mismatch between provider’s clinical judgement and meeting Loeb’s criteria. This finding may be explained by inadequate documentation and that the most commonly reported symptom (confusion) is not part of Loeb’s criteria. As a result, antibiotics were overprescribed potentially increasing rates of resistance. It is imperative for LTC providers to be familiar with identifying and documenting criteria in order to appropriately diagnose and treat urinary tract infections.
66-B Poster: Inappropriate Antibiotic Prescribing is Common within a Veterans Affairs Primary Care System

Presenter: Nathan Shively, Fellow  
Services/Clinical Epidemiology  
Infectious Diseases

Research Interest: Health Services/Clinical Epidemiology Infectious Diseases

Mentors: Brooke Decker MD, Cornelius Clancy MD

Funding Source: None

Authors: Nathan Shively MD, Deanna Buehrle PharmD, Cornelius Clancy MD, Brooke Decker MD

Introduction: Antibiotic overuse is a critical healthcare problem. More data are needed in outpatient settings to inform antimicrobial stewardship efforts. As part of a quality improvement initiative, the use of antibiotics in primary care clinics at the Veterans Affairs Pittsburgh Healthcare System (VAPHS) was reviewed.

Methods: Outpatient antibiotic prescriptions by VAPHS primary care providers (PCPs) from September 2015 – August 2016 were catalogued. A random sample of prescriptions was reviewed for indication and duration and compared to consensus guidelines. Antibiotic index was defined as the number of antibiotic prescriptions per 1,000 patients per year.

Results: Over the period reviewed, 3,880 acute antibiotic prescriptions were written by 76 PCPs caring for 40,734 patients (median panel 600 patients; range 33-1,547). The overall antibiotic index was 95. Most commonly prescribed antibiotics were azithromycin (25.8%), amoxicillin-clavulanate (13.3%), doxycycline (12.4%), amoxicillin (11%), and trimethoprim-sulfamethoxazole (10.6%). Fluoroquinolones represented 11% of prescriptions. A total of 316 prescriptions were reviewed. After exclusions, 300 were available for analysis. The most common indications for reviewed prescriptions were upper respiratory infection (28.3%), urinary tract infection (23%), skin and soft tissue infection (15.7%), and COPD exacerbation (6.3%). In 5.7% of cases, no reason for the prescription was listed. The overall rate of inappropriate antibiotic prescribing was 49.7%. Among reviewed cases for which an antibiotic was indicated, the prescribed agent was guideline-discordant in 24.5%. Guideline-concordant agents were given for a guideline-discordant duration in 36.8% of reviewed cases. A telephone encounter prompted 32.3% of prescriptions. No difference in prescription appropriateness was identified between physicians and Advanced Practice Providers. Opportunity for improvement was identified in 76% of reviewed prescriptions.

Conclusion: Substantial antibiotic overuse was observed. Improving concordance with guidelines for common prescribing indications is a major opportunity for antimicrobial stewardship. A peer comparison intervention is currently underway.
67-B Poster: A communication intervention aimed at medicine doctors and nurses improves patient satisfaction scores

Presenter: Jill Allenbaugh, Fellow
General Internal Medicine

Research Interest: Medical Education

Mentors: Carla Spagnoletti MD, MS

Funding Source: Frontline innovation Grant (Beckwith Institute)

Authors: Jill Allenbaugh MD, Jennifer Corbelli MD, MS, Laurie Rack DNP, RN, NEA-BC, Carla Spagnoletti MD, MS

Introduction: Patient satisfaction continues to play an ever-expanding role in healthcare, from reimbursement to hospital rating. However, effective strategies to improve Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) remain scarce. At the University of Pittsburgh Medical Center, a multidisciplinary patient experience committee aims to improve patient experiences through targeted interventions. The committee identified communication-specific HCAHPS scores, specifically for items “Doctors (nurses) explained things in a way you could understand,” as an area for intervention. We hypothesized a lack of adequate training in bedside communication and identification of poor health literacy as reasons for suboptimal communication scores. The aims of our study were to (1) develop a multidisciplinary curriculum to teach physicians and nurses to best deliver complex medical information and (2) evaluate the effectiveness of the curriculum by examining HCAHPS scores for doctor and nurse communication.

Methods: A clear health communication curriculum was developed for 112 internal medicine (IM) residents and 120 nurses from the general medicine wards. The curriculum was disseminated through 60-90 minute workshops that were facilitated by IM clinician educators and a nurse educator. The content included didactic teaching on health literacy, small group discussion and simulated videos of optimal communication skills during bedside rounds and the discharge process. Data was collected from 422 HCAHPS surveys from patients discharged from these wards over a 6-month period. We compared that percentage of “top-box” scores (corresponding to a rating of 9 or 10 on a 10-point scale) on communication items between 3 months pre and 3 months post curriculum.

Results: A total of 76 residents (participation rate 68%) and 80 nurses (participation rate 67%) who work in 5 wards across 3 hospitals attended. Percentage of “top-box” scores improved for all doctor and nurse communication-specific HCAHPS items after the intervention. Significant improvement was seen in the specific questions, “Doctors listened carefully to you” (66% to 77% p= 0.02), “Nurses explained things in a way you could understand” (59% to 73% p=0.003), “Nurses listened carefully to you” (62% to 70% p=0.018) and “Overall communication with nurses” (65% to 75% p=0.025).

Conclusion: Our data shows that a multidisciplinary clear communication curriculum with a focus on health literacy can significantly improve doctor and nurse communication specific HCAHPS scores at a large academic hospital. As communication skills are essential to providing quality patient care, our curriculum has value for any medical specialty or healthcare system seeking ways to improve the patient experience.
Poster Abstracts

68-B Poster: Resident Experiences with a Program to Support Academic Scholarship during Internal Medicine Residency Training

Presenter: Andrea Carter, Fellow General Internal Medicine
Research Interest: Medical Education

Mentors: Michael Fine MD
Funding Source: General Internal Medicine

Authors: Andrea Carter MD, Timothy Anderson MD, Keri Rodriguez PhD, Kristina Hruska BA, Shanta Zimmer MD, Carla Spagnoletti MD, Alison Morris MD, MS, Wishwa Kapoor MD, Michael Fine MD

Introduction: Scholarship is an essential component of residency training required by the Accreditation Council for Graduate Medical Education and identified by residents as influencing career choices and satisfaction. Leadership and Discovery (LEAD) is a program developed in 2012 as a component of the University of Pittsburgh Medical Center Internal Medicine (IM) Residency Program that requires all categorical residents to engage in mentored scholarship, generally carried out as a research project. The aims of this study were to compare the perceived value of LEAD among current and former participants and to identify facilitators and barriers to participation in the program.

Methods: Our study sought information from the first 4 classes of IM residents participating in LEAD, including former graduates (started residency in 2012 & 2013) and current residents (started residency in 2014 & 2015). We surveyed all participants and conducted qualitative focus groups of purposeful samples from each class. The emailed survey contained 5-point Likert-scale questions (from 1=very dissatisfied to 5=very satisfied) regarding overall satisfaction with LEAD and its influence on future research plans. A qualitative methods expert led 6, 60-minute focus groups (2 with graduates and 4 with current residents) to identify facilitators and barriers to participation and suggestions for improvement. Survey data were analyzed using Wilcoxon rank-sum and chi-square tests. Transcriptions of audiotaped focus groups were analyzed by 2 coders using the grounded theory approach of constant comparison.

Results: Of 106 eligible residents, 78 (74%) completed the survey. Graduates reported higher overall satisfaction with LEAD than current residents (median 3.5 vs 3.0, p=0.001). Graduates agreed more frequently than current residents that participating in LEAD increased their likelihood of conducting future research (19/40 [48%] vs 7/38 [18%), p=0.008). The 35 focus group participants (5-7 per group) discussed common themes across groups (n= # of focus groups where we identified the theme). The most common facilitators were the desire for research experience to increase fellowship competitiveness (n=6), using the residency advisor to identify a mentor (n=6), and the aid of advice from an experienced mentor (n=6). The most common barriers were time constraints from clinical duties (n=6) and unclear expectations (n=5). Suggestions for improvement were providing lists of available projects (n=5) and mentors (n=5) and clearly defining expectations (n=4).

Conclusion: Compared to current residents, graduates reported higher overall satisfaction with LEAD and were more likely to agree that participating increased their likelihood of doing future research. Programs to support resident scholarship within IM residency should provide clear expectations and lists of “shovel-ready” projects and mentors for residents who face time constraints during clinical training.
69-B Poster: Impact of Women’s Health Residency Tracks on Clinical Practice

**Presenter:** Amy Farkas, Fellow
General Internal Medicine

**Research Interest:** Medical Education

**Mentors:** Melissa McNeil MD, Sarah Tilstra MD

**Funding Source:** General Internal Medicine

**Authors:** Amy Farkas MD, Melissa McNeil MD, Erin Contratto MD, Brigid Dolan MD, Sarah Tilstra MD

**Introduction:** To address the need for women’s health training, internal medicine residencies have established women’s health tracks (WHT) as a model of training for those interested in developing a gender focus to their careers. There has been little assessment of the impact of these tracks on career outcomes. The objective of this study was to determine if the graduates of WHT have continued their focus on gender specific care in their clinical practice.

**Methods:** We conducted a multi-institutional survey of internal medicine WHT graduates starting in 2000 from the University of Pittsburgh, University of Alabama, and Northwestern University. To control for the impact of physician gender on clinical practice, we paired each WHT graduate with a non-women’s health track (NWHT) female graduate from the same residency. The online survey was designed to assess their incorporation of gender specific care into their practice. Descriptive statistics and statistical comparisons between WHT and NWHT graduates were performed using Fisher’s exact test and Wilcoxon rank-sum test.

**Results:** Out of the 216 graduates surveyed, 133 responded for a response rate of 61.6%. While our data did not meet statistical significance, there were differences between WHT and NWHT graduates. Among those who had completed training, WHT graduates were more likely to report being in primary care (40.9% vs 32.3%) and among those in primary care, 48.2% of WHT graduates reported a focus on women’s health within their practice compared to 30.0% of NWHT graduates. WHT graduates were more likely to report treating menopause (85.2% vs 70%) and eating disorders (63% vs 40%) and to address contraception (88.9% vs 80%) and preconception counseling (85.2% vs 70%). Additionally, 22.2% of WHT graduates reported inserting sub-dermal contraceptives and 14.8% reported placing intrauterine devices where none of the NWHT graduates reported performing these procedures. Among those in subspecialty practices, 20.5% of WHT graduates reported that their practice was focused on women’s health compared to 9.5% of NWHT graduates. Additionally, WHT graduates were more likely to report treating a women’s health specific condition (73.7% vs 57.1%). Examples of women’s health specific conditions treated including, fertility concerns, pregnancy issues, and counseling regarding contraception and teratogenic medications.

**Conclusion:** Despite a non-significant difference in reporting providing women’s health care, the domain of the WHT primary care providers is substantially broader than that of the NWHT. Additionally, subspecialty graduates of WHT are more likely than NWHT graduates to incorporate women’s health in their clinical practice.
**70-B Poster:** PRACTICE MAKES PERFECT: OPTIMIZING STUDENTS' GERIATRIC ASSESSMENT SKILLS

**Presenter:** Rachel Jantea, Fellow Geriatric Medicine  
**Research Interest:** Medical Education  
**Mentors:** Rollin Wright MD  
**Funding Source:** Health Research and Services Administration A

**Authors:** Rachel Jantea MD, James Pschirer PharmD, Catherine Grant DNP, Rollin Wright MD

**Introduction:** Active engagement and immediate application of new skills promote effective adult learning. We faced the challenge of equipping 195 health professions students with geriatric assessment skills during a week-long geriatrics course. To assess learning and proficiency achieved after a ½-day skills fair, we measured students' performance and interpretation of geriatric assessments in older people.

**Methods:** University of Pittsburgh third year medical, nurse practitioner, physical therapy, pharmacy, and communication sciences students attended 12 of 18 possible stations at a geriatric assessment skills fair. They then paired up to perform assessments selected by older participants at health fairs in 9 community-based independent/assisted living facilities. Students recorded their findings and interpreted the participant's level of risk for the health outcome associated with each assessment. Participants retained a copy of the form for their physicians. Using FREQ procedures (SAS), we measured the frequency of assessments performed and frequency of errors or failures to determine risk.

**Results:** 195 students performed 1,038 geriatric assessments (mean 5.3/student) for 209 participants (mean age 86). The most common assessments performed were orthostatic blood pressure (157), cognition (146), pain (90), gait (87), depression (85), and sleep quality (82). Least common were grief (n=10), advanced directive (25), and oral health (28). 37% of assessments resulted in a positive screen for a geriatric condition. Error in assessment or failure to determine risk occurred at a rate of 11% (0.56 errors/student). Assessments associated with the highest error rate were: orthostatic blood pressure (27%), FRAX calculation (21%), depression screening (18%), and gait assessment (13%). Errors were least frequent for grief, medication adherence, and oral health (all <1%).

**Conclusion:** Health sciences students rapidly develop basic proficiency in geriatric assessment by learning and practicing assessments in a skills fair, then immediately applying them at health fairs. Errors were more common in some assessments, which may require a different instructional approach or more direct supervision of the skill to improve technique and interpretation.
71-B Poster: Peer Review of Videoed Teaching Encounters: A Novel Method for Continuing Teaching Education

Presenter: Sarah Merriam, Fellow General Internal Medicine

Research Interest: Medical Education

Mentors: Deborah DiNardo MD, Melissa McNeil MD

Funding Source: Shadyside Foundation

Authors: Sarah Merriam MD, Melissa McNeil MD, Deborah Dinardo MD, Megan Hamm PhD

Introduction: Practicing clinicians are held to well-established standards for the ongoing maintenance of clinical knowledge through CME requirements. While no such standard exists for cultivation of teaching skills, this is an equally critical component of professional development for medical educators. In this qualitative study, we evaluated the acceptability and efficacy of a novel method for teaching skills development. Faculty reviewed self-selected video segments of peer teaching during small group sessions. Monthly sessions were moderated by a master educator who guided direct observation of and reflection upon observed teaching, including highlighting efficacious teaching methods.

Methods: Semi-structured post-curriculum telephone interviews were conducted with 20 of the 40 total participating faculty during summer 2016. We created an open-ended question script that was used by an experienced interviewer. The 20-minute interviews were audio-recorded, de-identified, and transcribed verbatim. Using the editing approach of qualitative analysis developed by Crabtree and Miller, a codebook was developed and refined. Two coders independently applied the codes to interview transcripts using ATLAS.ti (Scientific Software, Berlin Germany) software. After coding, discrepancies between coders were adjudicated until agreement was achieved. Original coding files prior to adjudication were used to calculate intercoder reliability. The mean Kappa statistic was 0.66.

Results: Seven senior faculty, 7 junior faculty and 6 medical education fellows were interviewed. Generally, interviewees viewed the curriculum positively. The most frequently cited advantages included: exposure to new teaching strategies, the ability to give/receive direct feedback, gaining a new perspective on individual teaching behavior, and the “safety” of the learning environment. Despite an overall endorsement of the curriculum, the following criticisms emerged: discomfort reviewing video, difficulty giving feedback across hierarchy, technology challenges. None described the curriculum as unsafe, critical or evaluatory. Most faculty reported incorporating (12/20) or planning to incorporate (6/20) a new teaching behavior into their practice. Twelve described an increase in self-reflective behaviors outside of curricular sessions. All interviewed would recommend the curriculum to other faculty and endorsed a plan for continued participation.

Conclusion: Though faculty development for the maintenance of teaching skills has been shown to be effective, formal programs are underutilized. This novel curriculum which focuses on direct observation of and reflection upon individual teaching encounters, is an effective, acceptable and efficient means to improve and expand the teaching practice of medical educators. This longitudinal, self-directed curriculum serves as a model for similar interventions at other academic institutions.
**72-B Poster:** Enhanced Care Program, A Model for Complex Care Management: Quality of Care Outcomes

**Presenter:** Swati Shroff, Fellow  
General Internal Medicine

**Research Interest:** Medical Education

**Mentors:** Gary Fischer MD,  
Wishwa Kapoor MD

**Funding Source:** General Internal Medicine

**Authors:** Swati Shroff MD

**Introduction:** Five percent of the population accounts for over half of healthcare expenditures in the US. Our innovation is the design and implementation of an Enhanced Care Program (ECP) to meet the needs of complex, high-utilizing individuals. The program aims to: reduce unnecessary healthcare utilization, improve quality of care, and improve the patient experience.

**Methods:** The ECP is being implemented in the University of Pittsburgh General Internal Medicine practice in Oakland (GIMO) in collaboration with UPMC Health Plan (UPMC-HP). Individuals are invited to participate if they meet the following criteria: 1) >1 inpatient hospitalization or >5 ED visits in previous year; 2) ≥18 years of age; 3) UPMC-HP member; 4) Receive primary care at GIMO; and 5) Agree to participate. The ECP is embedded within a patient centered medical home primary care practice. The primary ECP team consists of physicians, nurse care managers, and a secretary, with assistance from a pharmacist, psychologist, and psychiatrist. After individualized care plan development, patients have regular follow up with the team, including 24/7 direct telephone access, same day walk-in appointments and home visits. Quality of care outcomes include pre and post-ECP adherence to HgbA1C goals, blood pressure goals, and age-appropriate preventive care services after ≥6 months of ECP participation.

**Results:** From July 2014 to December 2016, 769 patients were screened, and 324 were eligible for the ECP. Of eligible patients, 194 were enrolled and 51 were withdrawn, leaving 143 actively enrolled patients. Of the 194 enrolled, 141 remained in the program for ≥6 months and were included in the quality data analysis if applicable. In hypertensive patients, blood pressure <140/90 improved from 54% to 68%. For diabetic patients, rates of HgbA1C <9 improved from 69% to 71%, foot exams 69% to 83%, eye exam 48% to 73%, and blood pressure <140/90 56% to 66%. Rates of cervical cancer screening improved from 79% to 86%, breast cancer screening 60% to 64%, and colorectal cancer screening 75% to 85%. The rate of patients with mental health illness linked to psychiatric care improved from 53% to 88%, and 20% of patients on chronic opioids were weaned off.

**Conclusion:** In high-utilizing patients enrolled in the ECP for ≥6 months, various quality of care outcomes, including blood pressure, diabetic control and cancer screening, have improved.
73-B Poster: An Innovative Patient Safety Curriculum For Pediatric Residents

Presenter: John Szymusiak, Fellow General Internal Medicine

Research Interest: Medical Education

Mentors: Hong Nguyen MD, Cornelius Clancy MD

Funding Source: General Internal Medicine

Authors: John Szymusiak MD, Catherine Polak MD, Kwonho Jeong MS, Doris Rubio PhD, Andrew Urbach MD, Stephanie Dewar MD, Michael Fox MD, Alda Maria Gonzaga MD

Introduction: Patient safety is important to resident education. A local needs assessment of pediatric residents showed that >93% agreed safety was important for their education and practice. Only 13% felt comfortable using root cause analysis (RCA) and 48% felt prepared to apply safety principles to future careers. By creating a formalized safety curriculum we aim to increase residents’ comfort applying safety principles, satisfaction with their safety education, knowledge of safety, and event reporting rates.

Methods: Senior residents were surveyed before and after the 5-month curriculum. Attitudes were assessed with a 5-point Likert scale and qualitative questions, knowledge with a multiple-choice test, and reporting behaviors by self-report. Residents with pre- and post-data were analyzed using the Wilcoxon matched-pairs signed-ranks test. Fisher’s exact test was used to see if attendees had improved attitudes and knowledge compared to non-attendees. Qualitative answers were analyzed thematically.

Results: Of 75 residents, 45 (60%) completed the pre-survey and 43 (57%) completed the post-survey, with 26 (35%) doing both. Of these, 15 (58%) attended curricular sessions and 11 (42%) had not. Attendees showed significant increases (p<.05) in their comfort with RCA, preparedness to apply safety to future practice, and curricular satisfaction. Non-attendees showed no significant attitudinal changes. More attendees had improved knowledge of how to report and comfort with RCA than did non-attendees (p<.05). There were no changes in knowledge scores or event reporting. Qualitative questions identified understanding the reporting process, RCAs, and follow-up on event reports as valuable parts of the curriculum. Residents desired more time to debrief about safety events.

Conclusion: Attendees showed improved attitudes and preparedness to apply safety to their future practice. This was not due to maturation as non-attendees showed no changes. Attendees did not show improved knowledge scores, possibly due to poor attendance or an overly challenging test. Attendees stated in qualitative questions that they would file more event reports. However, when asked how often they had actually reported there was no change from their pre-curricular reporting rates - it is worth exploring further residents’ perceived barriers to event reporting. Residents appreciate having a forum to vent and deal with the emotions involved in errors. This curriculum would be easily transferable to other specialties or institutions.
74-B Poster: Internal Medicine Residents’ Perceptions of Error Reporting: A Qualitative Study

Presenter: John Szymusiak, Fellow General Internal Medicine

Research Interest: Medical Education

Mentors: Greg Bump MD, Alda Maria Gonzaga MD, Maggie Benson MD

Funding Source: Thomas H. Nimick Competitive Research Fund

Authors: John Szymusiak MD, Thomas Walk MD, Maggie Benson MD, Megan Hamm PhD, Susan Zickmund PhD, Alda Maria Gonzaga MD, Greg Bump MD

Introduction: Event reporting is important for recognizing types of errors occurring in a hospital and ways to improve patient safety. Residents are frontline providers, yet little is known about their reporting attitudes. Our study aims to identify drivers and barriers to reporting among internal medicine residents at 2 tertiary care, academic institutions within our health-care system, and to identify modifiable aspects of an institution’s culture of safety that could encourage resident reporting. In so doing, we hope to improve patient care and promote career-long reporting in trainees.

Methods: Four focus groups were conducted, 2 at each hospital of interest, with senior-level internal medicine residents. Participants filled out a questionnaire with demographic information and assessing their reporting experience. They were then asked open-ended questions by a trained moderator based on a piloted focus group guide. All discussions were audio-recorded, de-identified, and transcribed verbatim. Using the “editing approach” to qualitative analysis a codebook was developed and applied independently by 2 trained coders.

Results: The 4 focus groups varied in size from 7 to 11 participants, with a total of 35 participants. Thirty-three residents completed demographic data, 18 (55%) were PGY-3. Thirty participants (91%) rated their knowledge of how to report as fair, good, or excellent. The barriers and drivers identified clustered into three categories. In the category of event related issues, barriers were when the event was due to someone else’s error or was reported in another forum; drivers were when the event was a system error or caused harm. In the category of cultural and institutional issues, barriers were differences in MD/RN perspective or when the system was viewed as “blame based”; drivers were attending encouragement and perceived potential for improvement. In the category of reporting system and process issues, barriers were a lack of anonymity and a lack of transparency of the process and consequences; drivers were follow-up on reports and visible changes to the system.

Conclusion: Focus groups are useful to understand residents’ attitudes about reporting. Interventions to encourage reporting can target each of the categories of drivers/barriers identified. These include showcasing system benefits of reporting others’ errors, educating all members of the multidisciplinary team about the goals and process of event reporting, having reports go to neutral third party safety officers to protect anonymity, and making event reporting follow up part of existing resident conferences. Similar interventions could prove effective at other academic institutions to improve resident engagement in patient safety.
**75-B Poster:** Back to the Bedside in the Outpatient Setting: Exam Room Presentations in Resident Continuity Clinic

**Presenter:** Rachel Vanderberg, Fellow General Internal Medicine

**Research Interest:** Medical Education

**Mentors:** Melissa McNeil MD, Carla Spagnoletti MD

**Funding Source:** General Internal Medicine, Shadyside CRF

**Authors:** Rachel Vanderberg MD, Melissa McNeil MD, Carla Spagnoletti MD

**Introduction:** Exam room presentations (ERPs) in resident continuity clinic (RCC) have the potential to meet several current needs in medical education including operationalizing ACGME Milestones through direct observation, improving patient satisfaction, and promoting patient-centered care. Prior studies suggest ERPs, defined as the initial case presentation and discussion in the exam room with both the patient and attending physician present, are beneficial for patients and learners. We suspect, however, the majority of case presentations in RCC take place away from the patient. We aimed to assess the current use of ERPs and barriers to ERPs in RCC.

**Methods:** General Internal Medicine faculty at the University of Pittsburgh who precept RCC were invited to complete a survey regarding ERPs. The survey asked them to rate 10 common perceptions about ERPs as not a barrier, somewhat of a barrier, or a significant barrier. Subsequently, faculty were invited to an ERP workshop and encouraged to pilot ERPs in RCC for one month. After the pilot period, faculty re-rated the perceptions. Perceptions rated as somewhat of a barrier or a significant barrier were considered barriers.

**Results:** The pre-survey response rate was 74% (26/35). The majority of faculty, 65%, reported never utilizing ERPs. The most frequently perceived barriers included learner discomfort, time, and ability to review the chart at 96%, 92%, and 81% respectively. The post-survey response rate was 71% (24/34) and 83% of the faculty indicated they tried at least one ERP. Learner discomfort, time, and ability to review the chart were rated as barriers by 71%, 83%, and 62% of the faculty respectively. Over half of the faculty felt that patient discomfort, attending physician discomfort, ability to write an attending attestation, and bedside teaching were not barriers to ERPs. Half of the faculty indicated they would continue to use ERPs. Time was the most frequently identified barrier in the post-survey. Additionally, time was the most substantial barrier as half of the faculty felt it was a significant barrier in both surveys. Several faculty identified urgent care appointments as an ideal venue for ERPs in the comments section of the survey.

**Conclusion:** The majority of presentations in RCC take place away from the patient. Time remained a substantial barrier to ERPs before and after the pilot period. Learner discomfort was less frequently perceived as barrier to ERPs after the pilot period.
**Poster Abstracts**

**76-B Poster:** Identification of a region within the Thrombospondin-1 Type III Domain with inhibitory activity against *P. aeruginosa* elastase activity

**Presenter:** William Bain, Fellow  
**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Janet Lee MD  
**Funding Source:** Multiple

**Authors:** William Bain MD, Jason Darell, Tolani Olonisakin BA, Yanyan Qu PhD, Joseph Pilewski MD, Janet Lee MD

**Introduction:** Pseudomonas aeruginosa is a gram-negative bacterial pathogen and a common cause of both hospital-acquired acute lower respiratory tract infection and chronic infections in those with structural lung disease. *P. aeruginosa* secretes multiple proteases, including *Pseudomonas* elastase (LasB), a zinc metalloproteinase, as a mechanism of virulence that promotes tissue injury and cell damage. Thrombospondin-1 (TSP-1) is a trimeric matricellular protein found primarily in platelet α-granules and released during inflammation. TSP-1 inhibits neutrophil serine proteases such as neutrophil elastase (NE) and cathepsin G (CG) through the type III repeats domain. A discrete region within TSP-1 type III repeats (T3R) domain can inhibit neutrophil NE and CG activity. We hypothesized that the T3R region of host matricellular protein TSP-1 shows inhibitory action against *P. aeruginosa* elastase LasB activity.

**Methods:** A 9-mer region of the type III repeats region (herein referred to as DV-9), corresponding to residues 793-801, was generated and compared with DP2-9, the same 9-mer with a single amino acid substitution at the fourth residue from a hydrophilic Q to a hydrophobic P. A 6-mer peptide corresponding to the type I region of TSP-1 was used as control. A previously reported specific di-peptide inhibitor against LasB (LasBI, N-mercaptoacetyl-Phe-Tyr-amide) was generated and used as reference. Purified *Pseudomonas* elastase was incubated in the presence or absence of DV-9, DP2-9, or LasBI and total elastase activity was quantified over time using a fluorogenic elastin substrate. Trials were completed in triplicate and the half maximal inhibitory concentration (IC50) of each compound was quantified.

**Results:** A di-peptide specific LasB inhibitor with reported Ki=41 nM against in vitro PA biofilm formation showed dose-dependent inhibition of *Pseudomonas* elastase activity with an IC50=3.87µM (95% CI: 1.81-8.28µM). DV-9 of the T3R of TSP-1 also inhibited *Pseudomonas* elastase activity in vitro in a dose-dependent fashion with an IC50=6.78µM (95% CI: 2.34-19.6µM). Substitution of polar glutamine with a hydrophobic proline at the fourth residue of DV-9 in DP2-9 peptide markedly reduced capacity to inhibit LasB (IC50=101µM; 95% CI: 52.3 - 195.2µM). 6-mer peptide showed no inhibitory activity against purified LasB.

**Conclusion:** A discrete region within the TSP-1 type III repeats domain previously shown to exhibit inhibitory activity against neutrophil granule serine proteases inhibits a structurally dissimilar metalloprotease *P. aeruginosa* LasB in vitro. Optimizing the backbone of this T3R peptide may provide the framework for a novel inhibitor with dual protection against pathogen encoded-exoprotease and host-derived proteases released during infection-induced injury.
**77-B Poster:** Alterations in the β-catenin pathway in non-small cell lung cancer defines a distinct molecular subtype with prognostic and therapeutic implications

**Presenter:** Saveri Bhattacharya, Fellow  
**Research Interest:** Translational Hematology/Oncology

**Mentors:** Timothy F. Burns MD, Laura P. Stabile PhD  
**Funding Source:** UPCI Lung Spore, UPMC Genomics, Initiative, CURE

**Authors:** Saveri Bhattacharya DO, Ashwin Somasundaram MD, Fei Ding MS, Autumn L. Gaither Davis MPH, Arjun Pennathur MD, William A. LaFramboise PhD, Sanja Dacic MD, PhD, Brenda F. Kurland PhD, Laura P. Stabile PhD, Timothy F. Burns MD, PhD

**Introduction:** The treatment of non-small cell lung cancer (NSCLC) has been revolutionized by the development of targeted therapy for distinct molecular subsets. Activation of the β-catenin pathway is essential for colorectal carcinoma tumorigenesis and has been implicated in hepatocellular, thyroid and ovarian cancer. The β-catenin pathway is involved in the cell adhesion complex and Wnt signaling. While mutations in this pathway have been reported in NSCLC and β-catenin overexpression correlates with worse survival, its role in lung tumorigenesis is poorly understood.

**Methods:** We performed targeted next generation sequencing using the Ion Torrent Hotspot Cancer Panel v.2 on tumor tissue from 244 NSCLC patients in which we have defined key demographic and clinical parameters including stage and survival. This cohort contained 91 Stage I cases with mRNA expression data using an Illumina platform. Co-occurrence of genes in the β-catenin pathway and 27 other genes in the panel were assessed by Fisher's exact test, with Benjamini-Hochberg adjustment for multiple comparisons.

**Results:** Seventeen of 244 tumors had mutations in the β-catenin pathway: 10/170 non-squamous NSCLC (6%, 95% CI 3%-10%), and 7/70 squamous NSCLC (10%, 95% CI 5%-19%). The rate of EGFR and RB1 mutations was higher in tumors with β-catenin pathway mutation (5/17 and 2/17) than in those without (13/227 and 0/227, adjusted p=0.06 for both). The presence of an APC mutation was also associated with higher expression of pro-survival protein, BCL2 (5/41 vs. 0/50, unadjusted p=0.022, adjusted p-value=0.3). Furthermore, APC mutations were more frequently observed in tumors with higher levels of EMT markers (high VIM 8% vs. low VIM 0%, unadjusted p=0.16) and EMT transcription factors (high ZEB1, ZEB2, TWIST1, TWIST2, SNAI1, SNAI2 10% vs. low expression 2%, unadjusted p=0.16). Finally, we observed a trend toward worse overall survival in non-squamous tumors with mutations in the β-catenin pathway (log rank test p= 0.07).

**Conclusion:** These studies suggest that tumors with β-catenin pathway alterations are defined by a more mesenchymal and potentially drug resistant subtype which portends a poor prognosis.
**Introduction:** The optimal timing, route, and level of caloric support in critically ill patients with sepsis remain unclear. We have previously demonstrated that early administration of low-level intravenous (IV) dextrose in an endotoxemic mouse model impairs glucose tolerance, lowers insulin sensitivity, and leads to profound hyperglycemia. Conversely, early administration of enteral dextrose increases insulin secretion, improves insulin sensitivity, and lowers inflammation. Given that endotoxemia is a sterile model of inflammation, we examined the impact of route of nutritional supplementation in a model of gram negative pneumonia. We hypothesized that enteral dextrose infusion will result in improved glucose tolerance and hemodynamics, reduced lung injury, and increased survival compared to IV dextrose infusion.

**Methods:** 10 week old C57BL/6 mice were randomized to receive enteral saline, IV dextrose, or enteral dextrose via femoral venous or gastric catheters (n=33). Immediately following catheterization, mice were inoculated with Klebsiella pneumoniae (KP, 2x10^4 CFU) via aspiration. Blood pressure and heart rate were monitored continuously. After 24 hours, saline or dextrose infusions were initiated (100 uL/hr, equivalent to 40% daily caloric requirements per day). Blood was sampled at 24 hour intervals starting at time of infusion to measure circulating blood glucose, insulin, and cytokines. Mice were sacrificed after 72 hours or if blood pressure dropped to <60 mmHg after which bronchoalveolar lavage (BAL) was performed for protein and cell count analysis.

**Results:** KP mice receiving IV dextrose had higher blood sugar, total BAL protein concentrations (536.5±61.7 ug/mL vs. 306.7±46.7 ug/mL, p<0.004), and proportion of neutrophils (26.77±4.8% vs. 18.88%±4.79%, p=0.05), compared to mice receiving enteral saline. In contrast, mice receiving an equal amount of enteral dextrose maintained normoglycemia and stable hemodynamics and demonstrated a lower proportion of neutrophils in BAL fluid (13.18±4.28%, p=0.05) compared to mice receiving IV dextrose. Finally, KP mice receiving enteral dextrose survived (72 hours) at a higher rate (60%) compared to KP mice receiving IV dextrose (0%) or enteral saline (20%).

**Conclusion:** Provision of early enteral dextrose attenuates inflammation, improves glucose regulation, and increases survival in a murine pneumonia model of sepsis.
**Introduction:** Acute Respiratory Distress Syndrome (ARDS) is an inflammatory process, often caused by sepsis, is a cause of respiratory failure associated with high mortality. Refractory hypoxia, seen in severe ARDS, is treated with veno-venous extra corporeal membranous oxygenation (ECMO) which increases inflammatory markers. New therapies are needed to improve outcomes in ARDS. Stem cells modulate the immune system and thereby influence inflammation. Data suggests infusion of bone marrow derived mesenchymal stem cells (B-MSCs) improves oxygenation and promotes recovery of pulmonary tissue in ARDS, while little is known about effects on cardiac tissue. There is a need for investigation into the use of BMSCs as adjunct therapy. One such emerging therapy is HemoLung, a low flow, single cannulation, CO2 removal system. We hypothesize treatment with ECMO will be associated with increased inflammation, greater cardiac mitochondrial dysfunction and evidence of cardiac dysfunction compared to those treated with Hemolung. Additionally, we hypothesize infusion of B-MSCs will at least partially mitigate inflammation, improve mitochondrial function and resolve cardiac dysfunction.

**Methods:** 50 sheep will be divided into 5 groups; E. coli endotoxin, lipopolysaccharide (LPS) alone; LPS and ECMO; LPS and Hemolung; LPS, ECMO and B-MSCs; LPS, Hemolung and B-MSCs. 10 sheep will be included in each group. LPS will be infused to induce ARDS. 1 hour after LPS infusion, the animals will be started on therapy according to their assigned group. Vital signs, hemodynamic measures, and blood samples will be collected at 1 hour intervals. Echocardiography, PV loops will be completed at baseline, 1 hour after LPS and at termination of the study. Necropsy will be completed six hours after infusion of LPS. Tissue samples will be harvested from lung and cardiac tissue.

**Results:** 15 Sheep have been included in analysis, 7 LPS alone and 8 LPS plus Hemolung. There were no differences in weight or baseline lab values. After infusion of LPS there was a decline in arterial oxygenation and blood pressure indicating ARDS and severe sepsis had been achieved. PV loops and echocardiographic data reflect declining cardiac output over the course of the study. The mitochondrial respiratory index was normal in all the animals evaluated to date.

**Conclusion:** Further analysis is needed after the completion of all experimental groups. The changes we see in PV loop values and echocardiographic measures are consistent with clinical hemodynamics. The preliminary mitochondria data shows mitochondrial function is not effected by LPS or Hemolung.
Introduction: Severe asthma (SA) makes up 5-10% of the 26.4 million US asthma patients, but accounts for nearly 50% of asthma spending due to poor disease control despite corticosteroid (CS) treatment. Our laboratory has shown that the Type-1 cytokine IFN-? is increased in ~50% of SA airways, and is associated with worsened lung function and poor CS response in a mouse SA model. CXCL10 is a key chemokine for recruiting IFN-?-secreting type-1 T-cells. We examined whether increased CXCL10 levels are associated with a type-1 inflammatory signature in SA and might contribute to steroid resistance.

Methods: CXCL10 mRNA levels were obtained by quantitative PCR (qPCR) from human bronchoalveolar-lavage (BAL) samples from the Severe Asthma Research Program (SARP), mouse whole lung homogenates and monocytic THP-1 cell line samples. Human clinical data were obtained from SARP. Mice were subjected to a house dust-mite allergen [HDM] mild asthma model [MMA] or to a severe asthma model [SA] combining HDM with cyclic-di-GMP. Glucocorticoid Response Element (GRE) activity was assessed by reporter assay with a transfected GRE-linked luciferase plasmid.

Results: Approximately 50% of patients with SA had elevated levels of CXCL10 that strongly correlated with IFN-? expression (r=0.6115, p<0.0001). While CXCL10-high patients had no significant differences in lung function or bronchodilator response, they had a higher incidence of steroid bursts in the prior year (86% v 26%, p<0.01). Mouse models showed higher levels of CXCL10 in a SA model compared to MMA (p<0.01) that was unaffected by CS. THP-1 cells treated with LPS could have CXCL10 induction suppressed by either CS pretreatment (simulating chronic CS use) or simultaneous treatment (simulating CS burst). However, IFN-? induction of CXCL10 was unchanged by simultaneous treatment and increased with pretreatment (Fig. 1). GRE-reporter assay showed no effect of IFN-? on CS induced transcription/translation by the GRE promoter.

Conclusion: CXCL10 expression is increased in a subset of asthma patients with SA who had increased oral steroid bursts suggesting poorly controlled disease. Furthermore, we show that IFN-?-induced CXCL10 expression is not only refractory to suppression by CS, but might actually increase with chronic steroid treatment. This can create a feed forward loop leading to further Type-1 CD4+-T-Cell recruitment, Type-1 inflammation and further CXCL10 production. Our work suggests a mechanism for steroid resistance that contributes to worsening disease in SA. Further work is needed to elucidate the molecular underpinnings with the goal to identify novel targets for future therapy.
**Poster Abstracts**

**81-B Poster:** Ceftolozane-tazobactam for the treatment of multidrug-resistant Pseudomonas aeruginosa infections: Clinical effectiveness and evolution of resistance

**Presenter:** Ghady Haidar, Fellow Infectious Diseases  
**Research Interest:** Translational

**Mentors:** M. Hong Nguyen MD  
Cornelius Clancy MD  
**Funding Source:** Multiple Grants

**Authors:** Ghady Haidar MD, Nathan Philips, Ryan Shields PharmD, Daniel Snyder MD, Shaoji Cheng MD, Brian Potoski PharmD, Yohei Doi MD PhD, Binghua Hao MD, Ellen Press MSc, Vaughn Cooper PhD, Cornelius Clancy MD, M.Hong Nguyen MD

**Introduction:** Data are limited on the use of ceftolozane-tazobactam and emergence of ceftolozane-tazobactam resistance during multi-drug resistant (MDR)-Pseudomonas aeruginosa infections.

**Methods:** We performed a retrospective study of 21 patients treated with ceftolozane-tazobactam for MDR-P. aeruginosa infections. Whole genome sequencing and quantitative real-time PCR were performed on longitudinal isolates.

**Results:** Median age was 58 years; 9 patients (43%) were transplant recipients. Median Simplified Acute Physiology Score-II (SAPS-II) was 26. Eighteen (86%) patients were treated for respiratory tract infections; others were treated for bloodstream, complicated intra-abdominal or complicated urinary tract infections. Ceftolozane-tazobactam was discontinued in one patient (rash). Thirty-day all-cause and attributable mortality rates were 10% (2/21) and 5% (1/21), respectively; corresponding 90-day mortality rates were 48% (10/21) and 19% (4/21). The ceftolozane-tazobactam failure rate was 29% (6/21). SAPS-II score was the sole predictor of failure. Ceftolozane-tazobactam resistance emerged in 3 (14%) patients. Resistance was associated with de novo mutations, rather than acquisition of resistant nosocomial isolates. ampC over-expression and mutations within the AmpC O-loop or H2 helix were identified as potential resistance determinants. In one patient, a resistant isolate over-expressed efflux pump genes mexY, mexB and mexD.

**Conclusion:** In this small study, ceftolozane-tazobactam was successful in treating 71% of patients with MDR-P. aeruginosa infections, most of whom had pneumonia. The emergence of ceftolozane-tazobactam resistance in 3 patients is worrisome, and may be mediated in part by AmpC-related mechanisms. More reports on treatment responses and resistance during various types of MDR-P. aeruginosa infections are needed to define ceftolozane-tazobactam’s place in the armamentarium.
**Poster: Using genetically well-characterized Carbapenem-resistant Enterobacteriaceae isolates by whole genome sequencing to identify spectrum of activity and therapeutic niches for ceftazidime-avibactam and imipenem-relebacamt**

**Presenter:** Ghady Haidar, Fellow Infectious Diseases

**Research Interest:** Translational

**Mentors:** M. Hong Nguyen MD, Cornelius Clancy MD

**Funding Source:** Multiple Grants

**Authors:** Ghady Haidar MD, Cornelius Clancy MD, Liang Cheng PhD, Palash Samanta MD, Ryan Shields PharmD, Barry Kreiswirth PhD, M. Hong Nguyen MD

**Introduction:** IMP-REL and CAZ-AVI are active against CRE expressing class A (KPC) and C β-lactamases. Unlike IMP-REL, CAZ-AVI is active against class D (OXA) β-lactamases. We recently demonstrated that KPC-3 mutations confer CAZ-AVI resistance, but reduce IMP MICs. ESBLs and porin mutations also contribute to CR. Understanding differences in IMP-REL and CAZ-AVI activity against E with various resistance mechanisms is crucial for optimal drug use.

**Methods:** MICs were determined by broth microdilution. Whole genome sequencing was performed by Illumina Miseq.

**Results:** 100 clinical E isolates were studied (72 K. pneumoniae (Kp), 18 Enterobacter spp, 9 E. coli, 1 K. oxytoca). KPCs were most common (n=84), followed by MBLs (n=7) and class D OXAs (n=4); 5 did not produce carbapenemase. 46 isolates had ESBLs. All isolates were resistant to both IMP and CAZ. REL and AVI reduced IMP and CAZ MICs by median 32- (0.5-256) and 128-fold (0.5-2048), respectively. As expected, IMP-REL and CAZ-AVI were inactive against MBL-producers, and CAZ-AVI (but not IMP-REL) was active against OXA-producers. Median IMP-REL and CAZ-AVI MICs against 5 mutant KPC-3-Kp isolates (2 D179Y, 2 D179Y/T243M, 1 V240G (corresponding to KPC-8)) were 0.25 and 128 µg/mL, respectively. 55 Kp isolates expressed KPC-2 (n=29) or wild-type KPC-3 (n=26). Major ompK36 porin mutations (IS5 promoter insertion or ins AA134–135 GD) were present in 21 isolates. Presence of KPC-2 or -3 did not correlate with either CAZ-AVI (median 1 and 2 µg/mL) or IMP-REL (median 0.5 and 1 µg/mL) MICs. In contrast, a major ompK36 mutation was directly correlated with higher IMP-REL MICs (p=0.001), and a major ompK36 mutation (p=0.02) and presence of an ESBL (p=0.049) were independently correlated with elevated CAZ-AVI MICs. IMP-REL MICs were = 1 µg/mL against 97% (58/60) of KPC-2, KPC-3 and mutant KPC-3 isolates.

**Conclusion:** IMP-REL and CAZ-AVI have overlapping spectra of activity, and niches in which each is superior. Both agents are highly active against KPC-2 and KPC-3 producing E. IMP-REL is active against CAZ-AVI-resistant Kp that express mutant KPC-3 variants. CAZ-AVI is active against OXA-producing CRE that are IMP-REL-resistant. Major ompK36 porin mutations in KPC-producing Kp increase MICs of IMP-REL and CAZ-AVI, and may emerge as important resistance determinants during treatment when the drugs are used more extensively. Understanding resistance mechanisms for clinical isolates may help clinicians employ IMP-REL, CAZ-AVI and other new β-lactam/β-lactamase inhibitor agents most effectively in patients.
**Introduction:** There is a growing literature of technology-assisted cognitive-behavioral therapy (CBT) interventions for psychiatric disorders such as depression and chronic illnesses such as pain. Such interventions have begun to be extended to other medical populations and settings (e.g., the primary care office and the home) but have not been tested in patients with end-stage kidney disease who are being treated at a hemodialysis (HD) facility. Thus, the objectives of the present study were: (1) to assess feasibility of a technology-assisted CBT intervention in patients treated with dialysis; (2) to pilot test the efficacy of the intervention in this patient population to reduce symptoms of depression, pain, and fatigue, and to increase quality of life; and (3) to assess patient satisfaction with the intervention.

**Methods:** Participants included 8 adults (mean age=58.7; 50% male) who were receiving dialysis at a local HD facility. Patients were screened for clinically-elevated levels of depressive symptoms, pain and/or fatigue (i.e., >3 on the PHQ-2 or >4 on the BPI or >24 on the FACIT-F). For 8-10 weeks, patients met with a therapist for approximately one hour a week during regularly scheduled HD sessions via a HIPAA compliant video-conferencing platform (Vidyo). Patients used a study tablet equipped with headphones and microphone. The intervention included CBT modules that have been tested to treat depression, fatigue, and pain. Patients completed health questionnaires at baseline and 3 months follow-up.

**Results:** At baseline, frequency of elevated symptoms was as follows: (1) 25% of patients had elevated depressive symptoms (CES-D>16); (2) 75% had elevated pain (BPI average pain>3); (3) 75% had high levels of fatigue (FACIT-F>24); and (4) 10% had elevations in all three symptoms. Patient acceptability, satisfaction, and adherence with the video-conferencing sessions was high; more than 95% completed all 8 prescribed sessions. The intervention was also well received by renal providers. No significant changes in depression, fatigue, or pain were observed at 3 months (Figure 1), although there was small improvement in SF-36 Physical Component Summary score [mean change=3±3, p=0.04]. Relevant lessons were learned from this pilot study, including how to improve screening, technology, and facilitation of the intervention.

**Conclusion:** Our technology-assisted CBT intervention for end-stage kidney disease patients was feasible, well-accepted and required minimal additional resources in the outpatient HD setting. Although our study was not powered to examine effectiveness of the intervention, we observed improvements in some patient-reported outcomes, which warrants further evaluation in larger clinical trials.
**Poster Abstracts**

84-B Poster: BIOMECHANICS OF RIGHT VENTRICULAR DIASTOLIC FUNCTION

**Presenter:** Sae Jang, Graduate Student Cardiology

**Research Interest:** Translational Cardiology

**Mentors:** Marc Simon MD

**Funding Source:** AHA, The Pittsburgh Foundation, Vascular Medicine Institute

**Authors:** Sae Jang BS, Rebecca R. Vanderpool PhD, Eugene Lapshin BS, Timothy N. Bachman MSc, Andrea Sebastiani BS, Jeff J. Baust BS, Sunaina Rustagi BS, Marc A. Simon MD

**Introduction:** Right ventricular (RV) diastolic function has been associated with outcomes for patients with pulmonary hypertension. However, the relationship between biomechanics and hemodynamics in the RV has not been studied.

**Methods:** RV pressure overload was induced in rats via pulmonary artery banding (PAB) such that systolic RV pressures were greater than 50 mmHg. At 3 weeks after banding, RV hemodynamics were measured using an admittance catheter. Biaxial mechanical properties (stress-strain relationship) of the RV free wall (RVFW) myocardium were tested (control n = 7, PAB n =5) to extrapolate longitudinal and circumferential elastic modulus in low and high strain regions (E1 and E2, respectively). RV diastolic function was determined as the Eed, obtained by fitting an exponential function $P = a(e^{ßV-1})$ and calculating $Eed = dP/dV = aße^{ß*EDV}$. Hemodynamic pressure and volume were used to estimate wall stress during the diastolic phase by modeling the RV as a sphere (wall stress = (Pressure * radius)/(2*thickness)). Statistical analysis was done with Mann-Whitney U test.

**Results:** PAB significantly increased Eed (control: 60.9 ± 25.9, PAB: 134 ± 33, $p = 0.010$). Longitudinal E1 was significantly increased in PAB vs control (control: 44.0 ± 13.9, PAB: 69.2 ± 13.9, $p = 0.048$) while there was no significant change in E2 in the longitudinal direction nor in E1 or E2 in the circumferential direction. Wall stress (control: 0.2-3 kPa, PAB: 0.1-4 kPa) estimated using the diastolic phase of the PV loop (control: 1-8 mmHg, PAB: 1-16 mmHg) corresponded to the E1 region of the stress-strain curve.

**Conclusion:** RV pressure overload in PAB rats resulted in an increase in diastolic myocardial stiffness reflected both hemodynamically by an increase in Eed, and biomechanically by an increase in longitudinal E1. Modest increases in tissue biomechanical stiffness are associated with large increases Eed. Hemodynamic measurements of RV diastolic function and can be used to predict biomechanical changes in the myocardium.
**85-B Poster:** Dysbiosis Associated With The Acute Respiratory Distress Syndrome: A Prospective Cohort Study in Adults.

**Presenter:** Georgios Kitsios, Fellow  
**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Bryan McVerry MD, Alison Morris MD, MS  
**Funding Source:** T32

**Authors:** Georgios Kitsios MD, Adam Fitch MS, Sarah Rapport MPH, Shulin Qin MD, John Evankovich MD, Katherine Fair BS, Seyed Nouraie MD, Janet Lee MD, Xiaoping Chen MS, Alison Morris MD, MS, Bryan McVerry MD

**Introduction:** Microbiome perturbations (dysbiosis) have been described to occur rapidly in patients with critical illness and in experimental models of the Acute Respiratory Distress Syndrome (ARDS). However, understanding of the potential impact of dysbiosis on ARDS progression and outcomes remains limited. The objective of this project was to examine for discriminating patterns of dysbiosis in patients with ARDS versus controls and prospective associations with ARDS severity and clinical outcomes.

**Methods:** We prospectively recruited mechanically ventilated patients within the Pittsburgh Acute Lung Injury Registry and Biospecimen Repository. We collected mouth swabs (oral), tracheal aspirates (lung) and stool/rectal swab samples (gut) on days 1, 3 and 7 from enrollment. Bacterial 16S rRNA gene sequencing (V4 region) and quantitative PCR were performed on clinical samples and reagent controls. Taxonomic analyses were performed using Qiime. We also utilized publicly available datasets of healthy control samples (Lung HIV and Human Microbiome Projects).

**Results:** 57 patients (22 with ARDS, 26 controls at-risk and 9 controls not at-risk for ARDS; mean age 57 years; 54% males) were included. The most common risk factors among patients with or at-risk for ARDS were pneumonia (46%) and extrapulmonary sepsis (33%), and 90% of patients received broad-spectrum antibiotics. By qPCR, there was no difference in lung bacterial load between ARDS and control patients, or between ARDS severity categories. Microbial communities across the three body sites had reduced alpha diversity (by Shannon index) at enrollment compared to healthy control datasets, with a non-significant declining trend over time (Figure). Oral and lung microbial communities were taxonomically overlapping but were different to gut microbiota throughout one week of critical illness (anosim test for weighted unifrac distances <0.0005). Tracheal aspirate sequencing showed dominance of concordant taxa to culture-defined pathogens in 75% of patients with culture-based diagnosis of pneumonia; in the remaining discordant cases, sequencing indicated alternative pathogens (e.g. Fusobacterium or Lactobacillus taxa). Culture-negative tracheal aspirates in ARDS patients were comprised of “oral”-origin taxa (e.g. Prevotella, Streptococcus) without evidence of “gut”-derived taxa enrichment. Development of gut community dominance by a single taxon (>30% relative abundance) was associated with incident acute kidney injury (p<0.05).

**Conclusion:** Next-generation sequencing analysis identifies dysbiosis in multiple body sites in patients with or at-risk for ARDS, shows significant concordance with cultures, and indicates the mouth of intubated patients as major origin of microbiota in the lungs of ARDS patients. Further study of host responses will help us clarify the physiologic impact of the observed microbial perturbations.
**86-B Poster:** Microbial Dysbiosis In Sepsis and Associated Clinical Outcomes

**Presenter:** Georgios Kitsios, Fellow  
Research Interest: Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Bryan McVerry MD, Alison Morris MD, MS  
Funding Source: None

**Authors:** Katherine Fair BS, Georgios Kitsios MD, Adam Fitch MS, Sarah Rapport MPH, Alison Morris MD, MS, Bryan McVerry MD

**Introduction:** Recent research has implicated the gut microbiome in sepsis, but we lack evidence on the functional impact and the clinical predictive utility of specific microbial perturbations. Our objectives were to define the composition and temporal evolution of the gut microbiome in patients with sepsis compared to controls, to examine its relationship to microbial communities in the mouth and lung, and assess for the relationship of dysbiosis on clinical outcomes.

**Methods:** Clinical, physiologic and microbiologic variables were collected from prospectively recruited critically-ill patients with and without sepsis from the Pittsburgh Acute Lung Injury Registry and Biospecimen Repository. Samples for microbial community analyses were collected from rectal swabs or stool (gut), oral swabs (mouth) and endotracheal aspirates (lung) on days 1, 3 and 7 from enrollment. Bacterial 16S ribosomal RNA sequencing was performed on the MiSeq platform of the variable region V4 on clinical samples and reagent controls. Microbial community analyses were performed using Qiime. Plasma host-response biomarkers (IL-6, IL-8, TNFa, IL-1b) were quantified with a Luminex assay.

**Results:** 57 patients (41 with sepsis, mean age 57 years, 39 males) were included, and a total of 57 rectal swabs and 29 stool samples were analyzed. Overall, gut microbiome samples had low alpha diversity (mean Shannon index 3.9 (1.5), about half of the observed in healthy gut microbiome) with a non-statistically significant declining trend overtime. Due to significant taxonomic differences between rectal and stool samples (p=0.003 for beta-diversity differences), we performed stratified analyses by rectal swab or stool sample types. We did not find any overall significant microbial community differences between patients with sepsis or septic shock and controls or associations with inflammatory host-responses. However, high Firmicutes phyla abundance in stool samples was associated with lower IL-1b plasma levels (p=0.01). Among 11 patients with bacterial infections confirmed by blood or sputum cultures, 8/11 (72%) had dominance of the lung communities by a concordant pathogen genus, and in three cases (Klebsiella, E.Coli and Saureus pneumonias) there was also dominance of gut communities (rectal swabs) by corresponding genera.

**Conclusion:** Gut dysbiosis is evident in critically-ill patients with and without sepsis. Rectal swabs may provide discordant representations of the gut microbiome compared to stool samples in critically-ill patients, yet they allow for detection of pathogenic sequences in bacterial pneumonias. Further research is needed to define the role of gut dysbiosis in sepsis and the clinical utility of pathogen detection in gut microbiome samples.
**Introduction:** The microbiome has been proposed to play a role in progression of idiopathic pulmonary fibrosis (IPF) based on bronchoalveolar lavage (BAL) analyses, but the microbiome of lung tissue in IPF has not been explored. In addition, infections may trigger acute exacerbations of IPF (AEIPF), but no study has used next-generation sequencing to determine the presence of non-cultivatable bacteria. We examined the lung tissue microbiome in IPF and AEIPF.

**Methods:** A case-control study comparing microbial communities in lung specimens from patients with end-stage IPF (at transplantation or post-mortem) to communities from lung tissue from organ donors not utilized for transplantation. We performed quantitative PCR (qPCR) of the 16S rRNA gene and sequencing of its V4 hypervariable region from microbial DNA. We analyzed sequence data against published BAL-based datasets of IPF and controls.

**Results:** IPF lungs from 33 patients (nine with AEIPF) harbored an extremely low biomass microbiome by qPCR, had higher alpha diversity and different taxonomic composition compared to 32 age-matched controls (p values <0.05). IPF lungs had an increased relative abundance of “skin” origin taxa, and lower abundance of “oral” taxa, indicating a low intrinsic biomass and likely detection of contaminants. There were no differences between AEIPF and chronic IPF. We observed limited taxonomic concordance between tissue-derived and BAL-based samples.

**Conclusion:** Our data do not support the presence of IPF-related microbial proliferation in fibrotic tissue or dysbiosis associated with AEIPF. Topographic heterogeneity of the tissue microbiome in IPF and differences between tissue and airway samples may explain these results.
**88-B Poster:** Development of a Severe Rat Model of Metabolic Syndrome, Pulmonary Hypertension, and Heart Failure with Preserved Ejection Fraction (PH-HFpEF)

**Presenter:** Andrea Levine, Fellow  
**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Mark Gladwin MD, Yen-Chun Lai PhD  
**Funding Source:** TPPG 2P01HL103455

**Authors:** Andrea Levine MD, Tim Bachman MS, Ana Mora MD, Mark Gladwin MD, Yen-Chun Lai PhD

**Introduction:** Pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (HFpEF) is the most prevalent cause of PH. Features of the metabolic syndrome are recognized as risk factors for developing PH-HFpEF. Our group has developed a two-hit model of PH-HFpEF, which combines endothelial injury using VEGF receptor blocker SU5416 in rats with features of the metabolic syndrome due to double leptin receptor defect (obese ZSF1). Although this SU5416/obese ZSF1 (Ob-Su) rat model closely recapitulates the cardiac phenotype of human PH-HFpEF, the severity of PH (right vascular systolic pressure, RVSP ~ 38 mmHg) is lower than in patients with PH-HFpEF (RVSP 46-51 mmHg). Here, we attempted to develop a more severe “three-hit” PH-HFpEF model in obese ZSF1 rats with the combined treatment of SU5416 and hypoxia.

**Methods:** Eight-week old male obese ZSF1 rats were single-injected with SU5416 (Sugen, 20 mg/kg), exposed to hypoxic condition (10% O2) for 3 weeks, and maintained under normoxic condition (total 14 weeks, n= 4-5, Ob-SuHx).

**Results:** The Ob-SuHx rats developed higher RVSP compared to lean rats, along with preserved EF and both RV and LV hypertrophy. However, the elevated pulmonary pressures (RVSP ~40 mmHg) in Ob-SuHx rats were neither additive nor synergistic following the combined treatment with SU5416 and hypoxia, as compared to rats exposed to either Ob-Su or SuHx (RVSP ~67 mmHg). Interestingly, SU5416/hypoxia-treated obese ZSF1 rats demonstrate lower fasting blood glucose levels (111 and 148 mg/dL at week 7 and 14, respectively) and improved glucose intolerance in comparison to obese ZSF1 rats or Ob-Su rats (266 and 294 mg/dL at week 7 and 14, respectively). Finally, early treatments with nitrite (100 mg/L) and metformin (300 mg/kg) at the time of SU5416/Hypoxia exposure reduced pulmonary pressures in the Ob-SuHx model of PH-HFpEF.

**Conclusion:** We could not develop a more severe rat model of PH-HFpEF with the “three-hit” approach combining SU5416, chronic hypoxia, and metabolic syndrome. Hypoxia and obese ZSF1 rats do not “interact” in the setting of Sugen to develop more severe disease. Chronic oral therapy of nitrite and metformin prevents elevated pulmonary pressures in the setting of metabolic syndrome related PH-HFpEF.
89-B Poster: Vascular Endothelial Growth Factor May Impair Pro-Chondrogenic Activity of Platelet-Rich Plasma on Human Adipose Stem Cells

Presenter: Jr-Jiun Liou, Graduate Student  
Research Interest: Translational

Mentors: Rocky Tuan PhD  
Funding Source: DOD

Authors: Jr-Jiun Liou MEng PhD, Rocky Tuan PhD

Introduction: Autologous cell-based repair of cartilage injury, e.g., autologous chondrocyte implantation (ACI), is limited by donor site morbidity and the need for ex vivo chondrocyte expansion. Mesenchymal stem cells (MSCs), which are more accessible and have extensive expansion and chondrogenic potential, represent an alternative cell type for cartilage repair. Platelet-rich plasma (PRP), a popular biologic-based treatment for injured/inflamed articular joint, has previously been shown to promote stem cell proliferation and tissue healing.

Methods: To test the effect of PRP on MSC chondrogenesis, MSCs were isolated from infrapatellar fat pad (IFP-ASCs) of arthroplasty donors and PRP was collected from anticoagulated human whole blood and activated with CaCl2. For pellet culture, IFP-ASCs were pelleted in chondrogenic medium supplemented with different PRP concentrations (1, 5, 10, and 20%) for different durations (1-, 3-, 7-, and 21-day pulse at the beginning of culture period). For 3D culture, IFP-ASCs were resuspended in methacrylated gelatin/hyaluronic acid and photopolymerized as hydrogel constructs.

Results: Our results showed that increasing duration of PRP exposure corresponded to decreased expression of collagen type II (COL2) and aggrecan (ACN), while varying PRP treatment duration did not affect DNA content, but proportionally decreased GAG/DNA content in IFP-ASC pellet cultures. Histological examination showed that increasing PRP treatment time led to decreasing deposition of cartilage-specific extracellular matrix in IFP-ASC pellets, including proteoglycans and COL2. Similar results were observed in 3D hydrogel cultures. As vascular endothelial growth factor (VEGF), a growth factor found in PRP, has been suggested to impair chondrogenesis and cartilage repair, its involvement in PRP action was tested here by examining the effect of VEGF immuno-neutralization in IFP-ASC pellet cultures. Our results showed that at day 7, ACN gene expression decreased in the PRP group but addition of anti-VEGF antibody ablated this reduction.

Conclusion: Taken together, our findings suggest that although PRP is reported to be beneficial for pain relief and joint function improvement, it may not enhance hyaline cartilage formation, likely due to the adverse effect of VEGF on chondrogenic differentiation.
**Poster Abstracts**

**90-B Poster:** Dose-seeking and efficacy study of pembrolizumab plus vemurafenib for therapy of advanced melanoma

**Presenter:** Yana Najjar, Fellow  
**Research Interest:** Translational Hematology/Oncology

**Mentors:** John Kirkwood MD, Lisa Butterfield PhD  
**Funding Source:** None

**Authors:** Yana Najjar MD, Lisa Butterfield PhD, Hassane Zarour MD, Ahmad Tarhini MD, Diwakar Davar MD, Yan Lin PhD, John Kirkwood MD

**Introduction:** Pembrolizumab (P) is approved for treatment of unresectable or metastatic melanoma. The immunological effects of BRAF inhibitors (BRAFi) include increased melanoma antigen expression and tumor lymphocyte infiltration. Markers of T cell exhaustion and PD-L1 expression are also increased. We hypothesize that P may improve the function and durability of TILs by blocking PD-1/PD-L1 signaling.

**Methods:** We designed a study of the combination of vemurafenib (V) and P for dose-selection evaluation of safety and efficacy. P is given at the standard dosage of 200 mg q3 weeks without modification, and V at 480 mg twice daily, 720 twice daily, or 960 mg twice daily. Using mTPI (modified toxicity probability interval), we will efficiently identify the dose recommended for an expanded efficacy cohort. The maximum dosage level of V at which limiting toxicity rate is under 33% will be considered the recommended phase II dose (RP2D). We will use the intermediate dosage of V (720 mg twice daily) as the starting point in the combination. We aim to accrue 50 patients to this study, with 30 patients in the efficacy cohort. Major eligibility criteria include BRAF V600E/K, presence of measurable disease, and stability of brain metastases for 4 weeks post treatment (if applicable), prior to initiating treatment. Patients will undergo CT scans on day 0, at week 9, and every 12 weeks subsequently. Patients will continue to receive treatment until disease progression or dose limiting toxicity, for up to 2 years. Patients will be evaluated for toxicity every 3 weeks using CTCAE version 4.0. Patients with biopsiable disease will undergo biopsies prior to treatment and at week 3. Blood for correlative studies will be taken from all patients at week 0, 3 and 9. The study's primary endpoints are the safety of the combination and overall response rate (ORR). Secondary endpoints include progression free survival (PFS) and overall survival (OS).

**Results:** Planned correlative studies include expression of PD-L1 and PD-1, levels of Treg, MDSC, T lymphocytes and inhibitory cytokines before and after treatment, in tumor parenchyma and in peripheral blood. Two of planned fifty patients have been enrolled. Both have had a partial response on therapy.

**Conclusion:** We anticipate that treatment with pembrolizumab and vemurafenib will be safe and well tolerated. In addition to efficacy endpoints, extensive correlative studies are planned. This trial will open at 3 other institutions through the Regional Melanoma Translational Consortium.
**Poster Abstracts**

**91-B Poster:** Fbxo3 V221I polymorphism protects against skeletal muscle atrophy in COPD

**Presenter:** M. Emmet O’Brien, Fellow  
Research Interest: Translational Pulmonary, Allergy and Critical Care Medicine  
**Mentors:** Jessica Bon Field MD, MS, Rama Mallampalli, MD  
Funding Source: RO1  
**Authors:** Emmet O’Brien MD, Yingze Zhang PhD, Bill Chen PhD, Frank Sciurba MD, Rama Mallampalli MD, Jessica Bon Field MD, MS

**Introduction:** Skeletal muscle atrophy is a common finding in chronic obstructive pulmonary disease (COPD) and is associated with progressive loss of exercise capacity, functional decline, and increased mortality. Fat-free body mass index (FFMI) can be used as a measure of sarcopenia and has been shown to correlate with COPD disease severity. Genetic and epigenetic phenomena may contribute to emphysema susceptibility and the observed clinical phenotype in individuals with COPD. We have recently identified a novel single nucleotide polymorphism (V221I) in the E3 ligase Fbxo3 that results in a loss of function mutation that protects against airflow obstruction, emphysema, and FEV1 decline in smokers. A member of the Skp-Cullin1-F box superfamily, Fbxo3 regulates TNF-receptor associated factor-6 (TRAF6) by targeting Fbxl2, an E3 ligase that ubiquitinitates TRAF6, for proteasomal degradation, thereby potentiating inflammatory signaling and increasing muscle atrophy. We hypothesized that the FBXO3(V221) polymorphism is protective against decline in fat-free body mass in smokers.

**Methods:** Study participants (n=358), were recruited from the University of Pittsburgh SCCOR cohort which includes current and former smokers aged >40, with a minimum 10 pack-year tobacco exposure. All data acquisition procedures were performed under a University of Pittsburgh Institutional Review Board-approved protocol with written informed consent. CT scans, dual-energy x-ray absorptiometry and spirometry was performed in each study participant. Multi-detector computed tomography of the chest was analyzed by quantitative density histogram parenchymal scoring. TaqMan SNP genotyping was performed using a specific primer and probe set on genomic DNA extracted from peripheral blood monocytes of study subjects.

**Results:** The Fbxo3(V221) polymorphism was found in 54/358 (15.1%) of subjects. Multivariate regression analysis revealed a significant increase in FFMI in those with the SNP following adjustment for gender, age, FEV1, and activity level, FFMI 18.8 vs. 19.6 kg/m2; p=0.038. When the Fbxo3(V221) polymorphism was analyzed by gender, the increase in FFMI was observed in males (FFMI 20.3 vs. 21.9 kg/m2; p=0.0006) but not in females (FFMI 16.9 vs. 17.0 kg/m2; p=0.84).

**Conclusion:** The results of this study demonstrate that the Fbxo3(V221) polymorphism is common in our study population. The increase in FFMI observed in subjects with the Fbxo3(V221) polymorphism indicates that Fbox3 may play a role in determining the clinical phenotype in smokers with COPD. Interestingly, Fbxo3(V221) was increased FFMI in males but not females in our study population, the mechanism of gender predisposition of this polymorphism warrants further investigation. The findings of this study may lead to new therapeutic modalities to prevent sarcopenia and functional decline in subjects with COPD in the future.
**Introduction:** Cardiovascular disease (CVD) is the leading cause of death in kidney disease (KD) despite aggressive management of traditional risk factors. As such, nontraditional risk factors have received attention as potential therapeutic targets. Systemic exposure of the microbiota-derived metabolite trimethylamine-N-oxide (TMAO), which is associated with poor CVD outcomes, increases in KD disproportionately to reductions in renal clearance. Flavin-containing monooxygenases (FMO) oxidize trimethylamine (TMA) to form TMAO and are an important class of drug metabolizing enzymes. We hypothesize that FMO activity is increased in the setting of KD, leading to increased TMAO formation. Therefore, we aimed to assess the effect of experimental KD on FMO activity using TMA as a substrate.

**Methods:** Microsomes were isolated from liver tissue of KD (5/6thnephrectomized) and control rats (n=7 and 6, respectively). Microsomal incubation conditions were optimized, then enzyme kinetics were determined and compared between groups. TMAO was measured via LC-MS, and formation rate of TMAO was used as an indicator of hepatic FMO activity. Also, in a subset of rats (n=3 KD, n=4 control), serum TMAO concentrations were determined at sacrifice, and exploratory 16S DNA sequencing of intestinal scrapings was performed to compare TMAO exposure and microbiomes.

**Results:** Metabolic formation of TMAO was significantly increased by 25.6% in KD compared to control rats (Vmax 67.09 ± 1.87 vs. 53.41 ± 2.25 µM/mg protein/hr, p<0.0001). No significant differences in Km were observed. No differences in Alpha and Beta diversity metrics were observed in the 16S DNA sequencing between KD and control intestinal scrapings. The median TMAO concentration was increased 16-fold in KD compared to control (64.35 vs. 3.78 µM, p<0.0385)

**Conclusion:** These results suggest that FMO activity increases in kidney disease and may contribute to dramatically increased systemic exposure of TMAO.
Introduction: Cytomegalovirus (CMV) is a significant opportunistic infection and cause of morbidity/mortality in lung transplant recipients (LTRs). The presence of multiple episodes of CMV viremia is associated with decreased survival in LTRs, and recent studies have shown that CD8+ T-cell proliferation and function are important in CMV infection control. CD8+ T-cell function has also been shown to be integral in the control of other herpesvirus, including Epstein-Barr Virus (EBV), and during the early immune response to tumorigenesis. The aim of this study is to determine if IPF LTRs are at increased risk for other herpesvirus disease, PTLD, and malignancy.

Methods: All LTRs from January 1, 2010 and December 30, 2015 were identified retrospectively. Explant pathology and pre-transplant progress notes were used to identify primary lung disease. CMV relapse was defined as two consecutive positive CMV PCRs within six months of discontinuing post-transplant CMV prophylaxis for D+/R+ LTRs and within six months of primary infection for D+/R- LTRs. Donor/recipient EBV status, EBV PCR data, outpatient progress notes, and hospital discharge summaries were reviewed. The rate of EBV viremia (defined as any positive EBV PCR), biopsy-proven PTLD, VZV disease, HSV disease, and any malignancy were calculated. Two-tailed Fisher’s exact test was used to evaluate for differences.

Results: 600 LTRs were reviewed; 93 were excluded due to death within 1 year post-transplant or were lost to follow up. 110 of the remaining 507 (21.7%) were IPF. 18 of the 507 (3.7%) had PTLD. When adjusting for EBV mismatch, the incidence of PTLD in IPF was 6/110 (5.5%) compared to 5/397 (1.3%) for all others (p = 0.016). 32 (29.1%) of the IPF patients developed non-PTLD malignancy compared to 56 (14.1%) of the non-IPF patients (OR 2.50, 95% CI: 1.52-4.12, p=0.0004). There were no differences in HSV or VZV disease.

Conclusion: IPF LTRs have an increased risk for CMV relapse, EBV-related PTLD, and other malignancies in the post-transplant setting. With recent studies showing the importance of telomere length in IPF TLRs on CD8+ T-cell proliferation and function in the control of CMV infection, further basic science research is needed to investigate if there is concomitant dysregulation of EBV and other malignancy-related immune responses.
Poster Abstracts

**94-B Poster:** Short Telomere Length Predicts Poor Cytomegalovirus Outcomes in Lung Transplant Recipients with Idiopathic Pulmonary Fibrosis

**Presenter:** Spencer Winters, Fellow

**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** John McDyer MD

**Funding Source:** RO1

**Authors:** Hannah Mannem MD, Iulia Popescu PhD, Spencer Winters MD, Christa Wagner BA, Christopher Ensor PharmD, Vidya Hanumanthu MSc, Swati Gulati MS, Christine Sanserino MS, Pali Shah MD, Mary Armanios MD, John McDyer MD

**Introduction:** Shortened telomeres are a known risk factor for idiopathic pulmonary fibrosis (IPF), and IPF is the most common phenotype of short telomere syndrome. Little is known about outcomes of patients with IPF and short telomeres post-lung transplant. Cytomegalovirus (CMV) is the most common opportunistic infection in lung transplant recipients (LTRs). Immunologically, T-cell proliferation differentiates high-risk patients who control CMV infection versus those who develop relapsing viremia, defined as two consecutive plasma polymerase chain reactions (PCRs) >200 copies/ml after discontinuation of antiviral therapy. We hypothesized that severely shortened telomeres in IPF LTRs were associated with poor clinical and immunologic control of CMV infection.

**Methods:** We evaluated telomere length in lymphocytes from IPF LTRs, as well as age-matched controls, and compared those with telomere length < or > 10th percentile. Flow cytometry was used to measure CMV specific T-cell proliferation using the carboxyfluorescein succinimidylic ester (CFSE)-dilution method. Clinical data was assessed for CMV outcomes regarding viral control and end-organ disease. Data was analyzed using non-parametric tests and Cox proportional hazards-modeling.

**Results:** In our cohort of 84 LTRs, 42 had IPF as the primary diagnosis, with a median age of 57 years old. 29/42 patients had age-adjusted telomere lengths <10th percentile, with 23 (79%) demonstrating relapsing CMV viremia in this group. 13 patients had telomere lengths >10th percentile for age, with only 4/13 (31%) showing relapsing CMV infection (p=0.02). Patients with severely shortened telomeres demonstrated a significantly faster time to CMV relapse (p = 0.04). CMV specific T-cell proliferation in response to phosphoprotein 65 (pp65) peptides was significantly greater in the patients who clinically controlled CMV infection and who had telomere length >10th percentile in both the CD8+ and CD4+ T-cell subsets (p=0.025 and 0.003 respectively).

**Conclusion:** Our data show an association between severely shortened telomeres and the risk of developing relapsing CMV viremia. We found CMV specific T-cell proliferation, an immune correlate of viral control, was decreased in patients with severely shortened telomeres. This suggests a physiologic defect in cell cycle progression, leading to impairment in host immunity. Taken together, our data suggest a distinct clinical phenotype of IPF patients post-lung transplant with short telomere syndrome and decreased capacity for CMV control. Recognizing LTRs with short telomere syndrome may facilitate risk-stratification for CMV, assist in clinical management post-transplant, and ultimately improve outcomes.
This program was produced by the Office of Academic Affairs of the Department of Medicine.

**Vice Chair of Clinical Research**  
Alison Morris MD, MS  
Professor of Medicine, Immunology, and Clinical and Translational Research  
Director, Center for Medicine and the Microbiome  
Vice Chair for Clinical Research, Department of Medicine  
UPMC Chair in Translational Pulmonary and Critical Care Medicine

**Vice Chair of Pre-Clinical Research**  
Flordeliza Villanueva MD  
Professor of Medicine  
Director, Non-Invasive Cardiovascular Imaging  
Director, Center for Ultrasound Molecular Imaging and Therapeutics

**Project Manager and Editor**  
Jimette Gilmartin  
Project Coordinator, Office of Academic Affairs

**Project Coordinator**  
Amy Flaugh  
Program Administrator, Center for Medicine and the Microbiome

**Photography**  
Gerri Acri  
Administrative Coordinator