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### APRIL 29, 2019 – CLINICAL RESEARCH: RESIDENTS
UNIVERSITY CLUB – BALLROOM B

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>5:00 pm</td>
<td>Registration &amp; Poster Viewing</td>
</tr>
<tr>
<td>5:30 pm</td>
<td>Welcome &amp; Opening Remarks</td>
</tr>
<tr>
<td></td>
<td><strong>Mark Gladwin MD</strong></td>
</tr>
<tr>
<td></td>
<td>Jack D. Myers Professor and Chair, Department of Medicine</td>
</tr>
<tr>
<td></td>
<td>Director, Pittsburgh Heart, Lung, and Blood Vascular Medicine Institute</td>
</tr>
<tr>
<td>5:45-6:15 pm</td>
<td>Oral Presenters</td>
</tr>
<tr>
<td>6:15-7:15 pm</td>
<td>RESIDENTS: Poster Viewing Session &amp; Discussion</td>
</tr>
<tr>
<td>7:15-7:45 pm</td>
<td>Guest Speaker Presentation: <em>A Journey of Serendipity</em></td>
</tr>
<tr>
<td></td>
<td><strong>Terence S. Dermody, M.D.</strong></td>
</tr>
<tr>
<td></td>
<td>Vira I. Heinz Professor and Chair, Department of Pediatrics</td>
</tr>
<tr>
<td></td>
<td>Professor of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine</td>
</tr>
<tr>
<td></td>
<td>Physician-in-Chief and Scientific Director, UPMC Children’s Hospital of Pittsburgh</td>
</tr>
<tr>
<td>7:45-8:15 pm</td>
<td>Oral Presenters</td>
</tr>
<tr>
<td>8:15 pm</td>
<td>Awards Presentation</td>
</tr>
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## Schedule of Events

### APRIL 30, 2019 – RESEARCH DAY

**BIOMEDICAL SCIENCE TOWER SOUTH FOYER, S-100, Victoria Hall 125**

<table>
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<th>Time</th>
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<tr>
<td>9:00 am</td>
<td><strong>Registration &amp; Continental Breakfast Available</strong>&lt;br&gt;<code>Biomedical Science Tower South Foyer &amp; S-100</code></td>
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<tr>
<td>9:30-11:30 am</td>
<td><strong>SESSION A:</strong>&lt;br&gt;<strong>Poster Viewing &amp; Judging</strong>&lt;br&gt;<code>Biomedical Science Tower South Foyer &amp; S-100</code></td>
</tr>
<tr>
<td>11:30 am</td>
<td><strong>Lunch Available</strong>&lt;br&gt;<code>Victoria Hall 125</code></td>
</tr>
<tr>
<td>12:00-1:00 pm</td>
<td><strong>Keynote Presentation: A Viral Trigger for Celiac Disease</strong>&lt;br&gt;<code>Victoria Hall 125</code>&lt;br&gt;<em>Terence S. Dermody, M.D.</em>&lt;br&gt;Vira I. Heinz Professor and Chair, Department of Pediatrics&lt;br&gt;Professor of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine&lt;br&gt;Physician-in-Chief and Scientific Director, UPMC Children’s Hospital of Pittsburgh</td>
</tr>
<tr>
<td>1:15-3:15 pm</td>
<td><strong>SESSION B:</strong>&lt;br&gt;<strong>Poster Viewing &amp; Judging</strong>&lt;br&gt;<code>Biomedical Science Tower South Foyer &amp; S-100</code></td>
</tr>
<tr>
<td>3:30-4:30 pm</td>
<td><strong>Oral Presenters</strong>&lt;br&gt;<code>Victoria Hall 125</code></td>
</tr>
<tr>
<td>4:30 pm</td>
<td><strong>Awards Presentation</strong>&lt;br&gt;<code>Victoria Hall 125</code></td>
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</table>
Terence S. Dermody, M.D.

Dr. Terence S. Dermody is the Vira I. Heinz Professor and Chair of Pediatrics at the University of Pittsburgh School of Medicine and Physician-in-Chief and Scientific Director at UPMC Children’s Hospital of Pittsburgh where he leads a team of over 300 faculty members. He also is Professor of Microbiology and Molecular Genetics at the University of Pittsburgh School of Medicine.

Dr. Dermody received his B.S. degree from Cornell University and his M.D. degree from Columbia University. He completed an internal medicine residency at Presbyterian Hospital in New York and fellowships in infectious diseases and molecular virology at Brigham and Women’s Hospital and Harvard Medical School. Prior to moving to Pittsburgh in 2016, Dr. Dermody was Dorothy Overall Wells Professor of Pediatrics and Director of the Medical Scientist Training Program and Division of Pediatric Infectious Diseases at Vanderbilt University School of Medicine.

With over 32 years of experience in basic virology and viral pathogenesis research, at his core, Dr. Dermody is a virologist. Most of his research has focused on reovirus, an important experimental model for studies of viral encephalitis in the young, and chikungunya virus, an emerging mosquito-borne virus that causes epidemics of fever and arthritis. His research contributions have enhanced an understanding of how these viruses enter into host cells and cause organ-specific disease. He has published more than 240 articles, reviews, chapters, and editorials and has been recognized for his research accomplishments by the Vanderbilt Ernest W. Goodpasture Faculty Research Award, an NIH MERIT Award, and the American Society for Microbiology D. C. White Research and Mentoring Award.

Dr. Dermody is a member of the American Academy of Microbiology, American Pediatrics Society, American Society for Clinical Investigation, Association of American Physicians, and Society for Pediatric Research and a fellow of the American Association for the Advancement of Science. He is a past president of the American Society for Virology, past chair of the AAMC GREAT Group M.D.-Ph.D. Section Steering Committee, and past chair of the Virology Division of the International Union of Microbiological Societies. Dr. Dermody is an editor for the Journal of Virology and mBio and an associate editor for the Annual Review of Virology. He is a member of the Board of Directors of the Burroughs Wellcome Fund.
Oral Presenter – April 29, 2019
Michael Bashline, MD
PGY-3 Resident – Clinical Research

Bio: Michael is a third year categorical Internal Medicine resident at the University of Pittsburgh Medical Center. He was born and raised here in Pittsburgh, PA, where he completed his undergraduate training in Biomedical Engineering at the University of Pittsburgh. After deciding to pursue a career in medicine, he obtained his M.D. degree at Temple Medical School in Philadelphia, PA before returning to Pittsburgh for residency. He will be staying at UPMC to complete a fellowship in Cardiology and has been fortunate to have Dr. Marc Simon as a mentor. Outside of medicine, he keeps busy by spending time with his two young children, traveling, and running.

Presentation: The Effects of Inhaled Sodium Nitrite on Pulmonary Vascular Impedance in Patients with Pulmonary Hypertension Associated with HFpEF

Summary: Pulmonary hypertension (PH) is caused by a heterogenous group of disorders that results in an elevated pressure in the pulmonary vascular system due to changes in the pulmonary arteries ultimately leading to right ventricular (RV) failure and death. While Group 2 PH due to left heart disease (defined hemodynamically as resting mean pulmonary artery pressure [MPAP] of ≥ 25 mmHg and a pulmonary capillary wedge pressure [PCWP] > 15 mmHg) is the most common form and has been associated with poor outcomes in patients with heart failure with preserved ejection fraction (HFpEF), there is no approved treatment for these patients. Clinically, the hemodynamic severity of PH has typically been assessed by measuring the pulmonary vascular resistance (PVR). However, PVR is a steady-state measurement and ignores the highly pulsatile nature of the pulmonary vascular system, which has been shown to contribute up to one-third to one-half of the hydraulic load that the RV faces. Therefore, it is important to accurately measure the full afterload that the RV faces since this has been shown to be a major determinant of functional status, exercise capacity, development of heart failure, and risk for mortality in patients with PH. Pulmonary vascular impedance (PVZ) has been demonstrated in several studies to represent a more accurate depiction of the entire pulmonary vascular system by including both steady state and pulsatile forces, and is defined as the ratio of pressure to flow waves in the frequency domain. Our group previously published a phase IIa trial of the acute hemodynamic effects of inhaled nitrite on patients with Group 2 PH due to HFpEF (PH-HFpEF) showing an improvement in pulmonary artery compliance without a significant reduction in PVR. The objective of this study was to further elucidate the acute physiologic effect of inhaled nitrite on the RV afterload in PH-HFpEF as described by PVZ.

Methods: Patients meeting hemodynamic criteria for PH-HFpEF (MPAP ≥ 25 mmHg, PCWP > 15 mmHg, and transpulmonary gradient [TPG ] > 12 mmHg) underwent a standard right heart catheterization using a balloon-tipped thermodilution 7F Swan-Ganz catheter via the right internal jugular vein. Aerosolized sodium nitrite at a dose of 45 mg was administered followed by measurements of cardiopulmonary hemodynamics (right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output) every 15 minutes for 1 hour. This was then followed by a second dose of 90 mg aerosolized sodium nitrite with measurements of cardiopulmonary hemodynamics every 15 minutes for another hour before conclusion of study. Immediately prior to the first dose of sodium nitrite and immediately after the last hemodynamic measurement, pulmonary artery pressure was recorded.
simultaneously with transthoracic echocardiographic doppler imaging of the velocity through the pulmonary artery in the parasternal short axis view. Blood flow was calculated from Doppler velocity and the diameter of the pulmonary artery. A Fourier transform was then used to calculate the PVZ spectrum using MATLAB to deconstruct pressure and flow waves into their sinusoidal components for the first 10 harmonics. A representative graphic illustrating this process is shown in Figure 1. A Wilcoxon signed-rank test analysis was used as a non-parametric analysis to compare the variables pre and post-nitrite for significance and a p-value < 0.05 was used to determine statistical significance.

**Results:** Of twenty patients enrolled in the phase IIa study, fourteen had adequate data for this PVZ analysis. Two patients only received one dose (45 mg) of aerosolized sodium nitrite due to a drop in BP meeting predefined stopping rules. Figure 2 illustrates the impedance at the first 10 harmonics comparing pre-sodium nitrite to post-sodium nitrite administration. It shows a reduction in the impedance moduli of $Z_0$, which represents PVR since this is the ratio of mean pressure to mean flow, as well as a reduction in the first 6 harmonics after the administration of inhaled sodium nitrite. Table 1 lists the median along with 95% CI for each relevant variable before and after the administration of inhaled sodium nitrite. Inhaled sodium nitrite significantly decreased the characteristic impedance, $Z_C$ (1.23 dyne*sec/cm$^2$ to 0.81 dyne*sec/cm$^2$, $P = 0.04$), which has been shown to be inversely proportional to pulmonary artery compliance and represents the absence of wave reflections. Inhaled sodium nitrite significantly reduced the total work ($W_T$) performed by the RV (722 mW to 549 mW, $P = 0.04$), and improved RV efficiency, defined by a reduction in the total work divided by cardiac output, $W_T/CO$ (111 mW/mL*sec to 78 mW/mL*sec, $P = 0.004$). There were trends towards decreases in pulmonary vascular resistance ($Z_0$), first harmonic impedance ($Z_1$), steady state work ($W_s$), oscillatory work ($W_0$) and pulmonary vascular stiffness ($Z_0$) after administration of inhaled sodium nitrite although these reductions were not significant.

**Figure 1: Calculating Pulmonary Vascular Impedance**

**PA velocity (flow)**

**PA pressure – Tracings**

**Fourier Transform**

**Impedance**

$Z_0$, $Z_1$ and $Z_C$
Figure 2: Pulmonary Vascular Impedance Spectra of Inhaled Sodium Nitrite

Table 3: Effects of Inhaled Sodium Nitrite on Various PVZ Variables

<table>
<thead>
<tr>
<th>Characteristic Impedance, $Z_c$ (dyne*sec/cm$^5$)</th>
<th>Pre-Nitrite Median*</th>
<th>Post-Nitrite Median*</th>
<th>P-Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV Efficiency, $W_T/CO$ (mW/mL*sec)</td>
<td>111 (91-128)</td>
<td>78 (73-103)</td>
<td>P = 0.004</td>
</tr>
<tr>
<td>Total Work, $W_T$ (mW)</td>
<td>722 (598-820)</td>
<td>549 (468-781)</td>
<td>P = 0.041</td>
</tr>
<tr>
<td>Oscillatory Work, $W_o$ (mW)</td>
<td>185 (115-192)</td>
<td>154 (105-186)</td>
<td>P = 0.638</td>
</tr>
<tr>
<td>Steady State Work, $W_s$ (mW)</td>
<td>558 (465-646)</td>
<td>405 (344-614)</td>
<td>P = 0.064</td>
</tr>
<tr>
<td>Pulmonary Vascular Resistance, $Z_0$ (dyne*sec/cm$^5$)</td>
<td>5.95 (4.81-7.34)</td>
<td>5.58 (4.03-6.14)</td>
<td>P = 0.074</td>
</tr>
<tr>
<td>Pulmonary Vascular Stiffness, $Z_s$ (dyne*sec/cm$^5$)</td>
<td>2.69 (1.84-3.70)</td>
<td>2.03 (1.60-3.35)</td>
<td>P = 0.064</td>
</tr>
<tr>
<td>Wave Reflection Coefficient, $\Gamma$</td>
<td>0.311 (0.249-0.418)</td>
<td>0.313 (0.200-0.438)</td>
<td>P = 0.552</td>
</tr>
<tr>
<td>First Harmonic Impedance, $Z_1$ (dyne*sec/cm$^5$)</td>
<td>1.42 (1.01-1.90)</td>
<td>1.06 (0.82-1.68)</td>
<td>P = 0.064</td>
</tr>
<tr>
<td>$F_{min}$</td>
<td>2 (1.44-2.56)</td>
<td>2 (1.57-2.43)</td>
<td>P = 0.236</td>
</tr>
</tbody>
</table>

N = 14 patients
* Median (95% CI)
** P value with < 0.05

Conclusion: Pulmonary vascular impedance analysis showed that inhaled sodium nitrite acutely improves pulmonary vascular compliance by reducing characteristic impedance ($Z_c$) more so than PVR ($Z_0$) in patients with PH-HFpEF. Inhaled sodium nitrite was associated with improved RV efficiency and total work performed by the RV. These results suggest that inhaled sodium nitrite preferentially acts on
the larger, more proximal compliance vessels, rather than the smaller, distal vessels that contribute to resistance, to reduce the load on the right ventricle.

References:
Saloni Kapoor, MBBS

PGY-1 Resident – Clinical Research

Bio: Saloni is a categorical internal medicine intern and plans to pursue a career in interventional cardiology. She grew up in Jaipur, a colorful town in western India and went to medical school at All India Institute of Medical Sciences in Delhi. Before coming to UPMC she trained in an ophthalmology residency program for a year. Saloni works with Dr. Suresh Mulukutla in Cardiology evaluating outcomes in multivessel coronary artery disease using registry-based analyses. In her free time, she enjoys riding her bike on the trails of Pittsburgh and can be spotted sporting shirts with eccentric prints.

Presentation: Surgical Risk Stratified Outcomes in Coronary Bypass Versus Percutaneous Revascularization in Multivessel Coronary Artery Disease

Summary: The choice of coronary artery bypass graft surgery (CABG) versus percutaneous coronary intervention (PCI) among patients with multivessel coronary artery disease (MVCAD) or left main disease continues to be a clinical challenge. Data from both randomized and observational studies suggest that CABG should be preferred over PCI in MVCAD (1-6), and this is reflected both in US and European guidelines which recommend CABG for patients with 3-vessel or 2-vessel disease with proximal left anterior descending artery disease (Class I); however, the US guidelines still recommend PCI as an option of uncertain benefit (Class IIb) in this population (7-8). Despite this, several studies have noted a marked shift over the last 15 years from CABG to PCI as the revascularization strategy of choice (9-15). PCI is being offered to population cohorts that were not part of trials, especially those deemed to have high surgical mortality. Society of Thoracic Surgery score predicts perioperative mortality for CABG. We sought to examine how surgical risk affected outcomes in patient undergoing PCI vs CABG in MVCAD.

Methods: Patients from within the University of Pittsburgh Medical Center healthcare system who underwent CABG or PCI between 2010 and 2018 and for whom data was available through the National Cardiovascular Disease Registry (NCDR) or STS Registry were included. Patients were eligible to be included in the CABG arm if they had isolated CABG and in the PCI arm if they had either 3-vessel coronary disease defined by the presence of ≥70% stenosis in all 3 major coronary vessels, left main coronary stenosis of ≥50% severity, or 2-vessel coronary disease defined by the presence ≥70% stenosis in 2 major coronary vessels including the proximal left anterior descending artery. Exclusion criteria including prior CABG, STEMI presentation, staged revascularization, and lack of follow-up information. Surgical risk was assessed using STS score and classified patients into low (<4%), intermediate (4-8%) and high (>8%) risk. The primary outcome was mortality at 5 years and survival was assessed using the electronic health record and the United States Social Security Death Index. Secondary outcomes included freedom from inpatient readmission and freedom from repeat revascularization, excluding staged procedures.

Results: There were 6946 patients in the original dataset including 1891 who underwent PCI and 5055 CABG for MVCAD. The propensity-matched cohort included 844 in each group. Table 1 shows the baseline data for the propensity-score matched cohorts. Complete revascularization was a variable placed in the propensity-matched model and was not different between the PCI and CABG groups.
Table 2 shows outcomes for PCI and CABG cohort stratified by surgical risk. In the low risk cohort mortality, readmission and revascularization rates at 5 years were significantly (p<0.01) higher in the PCI group. In the intermediate risk cohort, CABG group had a statistically significant mortality benefit but did not reach significance in readmission and revascularization rates. In the high risk group no statistically significant difference was noted between PCI and CABG cohorts.

Table 1. Baseline Characteristics Revascularization Strategy for Propensity-Matched Cohort

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PCI</th>
<th>CABG</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td># Patients</td>
<td>1,688</td>
<td>844</td>
<td>844</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>67.4 ± 11.1</td>
<td>67.5 ± 12.0</td>
<td>67.2 ± 10.3</td>
<td>0.519</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.427</td>
</tr>
<tr>
<td>Male</td>
<td>1177 (69.7%)</td>
<td>596 (70.6%)</td>
<td>581 (68.8%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>511 (30.3%)</td>
<td>248 (29.4%)</td>
<td>263 (31.2%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.641</td>
</tr>
<tr>
<td>White</td>
<td>1531 (90.7%)</td>
<td>766 (90.8%)</td>
<td>765 (90.6%)</td>
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<tr>
<td>Black</td>
<td>101 (6.0%)</td>
<td>53 (6.3%)</td>
<td>48 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>56 (3.3%)</td>
<td>25 (3.0%)</td>
<td>31 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>30.3 ± 6.09</td>
<td>30.2 ± 6.20</td>
<td>30.3 ± 5.99</td>
<td>0.574</td>
</tr>
<tr>
<td>BSA</td>
<td>2.00 ± 0.25</td>
<td>2.00 ± 0.25</td>
<td>2.00 ± 0.24</td>
<td>0.787</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>355 (21.0%)</td>
<td>182 (21.6%)</td>
<td>173 (20.5%)</td>
<td>0.591</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>320 (19.0%)</td>
<td>166 (19.7%)</td>
<td>154 (18.2%)</td>
<td>0.456</td>
</tr>
<tr>
<td>Diabetes</td>
<td>800 (47.4%)</td>
<td>397 (47.0%)</td>
<td>403 (47.7%)</td>
<td>0.770</td>
</tr>
<tr>
<td>Dialysis</td>
<td>67 (4.0%)</td>
<td>35 (4.1%)</td>
<td>32 (3.8%)</td>
<td>0.708</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1478 (87.6%)</td>
<td>742 (87.9%)</td>
<td>736 (87.2%)</td>
<td>0.658</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1457 (86.3%)</td>
<td>733 (86.8%)</td>
<td>724 (85.8%)</td>
<td>0.524</td>
</tr>
<tr>
<td>Prior Liver Disease</td>
<td>85 (5.0%)</td>
<td>38 (4.5%)</td>
<td>47 (5.6%)</td>
<td>0.317</td>
</tr>
<tr>
<td>Prior Cancer</td>
<td>288 (17.1%)</td>
<td>149 (17.7%)</td>
<td>139 (16.5%)</td>
<td>0.518</td>
</tr>
<tr>
<td>Prior PAD</td>
<td>316 (18.7%)</td>
<td>161 (19.1%)</td>
<td>155 (18.4%)</td>
<td>0.708</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>343 (20.3%)</td>
<td>181 (21.4%)</td>
<td>162 (19.2%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Prior HF</td>
<td>276 (16.4%)</td>
<td>135 (16.0%)</td>
<td>141 (16.7%)</td>
<td>0.693</td>
</tr>
<tr>
<td>Prior MI</td>
<td>765 (45.3%)</td>
<td>371 (44.0%)</td>
<td>394 (46.7%)</td>
<td>0.261</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>635 (37.6%)</td>
<td>324 (38.4%)</td>
<td>311 (36.8%)</td>
<td>0.514</td>
</tr>
<tr>
<td>Cardiac Presentation</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No Symptoms or Angina</td>
<td>235 (13.9%)</td>
<td>117 (13.9%)</td>
<td>118 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>Symptoms Unlikely Ischemic</td>
<td>20 (1.2%)</td>
<td>11 (1.3%)</td>
<td>9 (1.1%)</td>
<td></td>
</tr>
<tr>
<td>Stable Angina</td>
<td>238 (14.1%)</td>
<td>119 (14.1%)</td>
<td>119 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>697 (41.3%)</td>
<td>355 (42.1%)</td>
<td>342 (40.5%)</td>
<td></td>
</tr>
<tr>
<td>Non-STEMI</td>
<td>469 (27.8%)</td>
<td>242 (28.7%)</td>
<td>227 (26.9%)</td>
<td></td>
</tr>
<tr>
<td>Angina Equivalent</td>
<td>7 (0.4%)</td>
<td>0 (0.0%)</td>
<td>7 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>22 (1.3%)</td>
<td>0 (0.0%)</td>
<td>22 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Left Ventricular Ejection</td>
<td>49.4 ± 13.2</td>
<td>49.7 ± 12.7</td>
<td>49.0 ± 13.7</td>
<td>0.275</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.30 ± 1.33</td>
<td>1.33 ± 1.40</td>
<td>1.27 ± 1.25</td>
<td>0.335</td>
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**Glomerular Filtration Rate**

<table>
<thead>
<tr>
<th></th>
<th>PCI Cohort</th>
<th>CABG Cohort</th>
<th>Chi-Sq P-Value</th>
<th>PCI Cohort</th>
<th>CABG Cohort</th>
<th>Chi Sq P-Value</th>
<th>PCI Cohort</th>
<th>CABG Cohort</th>
<th>Chi Sq P-Value</th>
</tr>
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<tbody>
<tr>
<td>Number of Diseased Vessels</td>
<td>1</td>
<td>23 (1.4%)</td>
<td>0 (0.0%)</td>
<td>23 (2.7%)</td>
<td>&lt;0.001</td>
<td>2</td>
<td>602 (35.7%)</td>
<td>309 (36.6%)</td>
<td>293 (34.7%)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1052 (62.3%)</td>
<td>530 (62.8%)</td>
<td>522 (61.8%)</td>
<td>0.565</td>
<td>3</td>
<td>1052 (62.3%)</td>
<td>530 (62.8%)</td>
<td>522 (61.8%)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>11 (0.7%)</td>
<td>5 (0.6%)</td>
<td>6 (0.7%)</td>
<td>0.565</td>
<td>Complete Revascularization</td>
<td>750 (44.4%)</td>
<td>367 (43.5%)</td>
<td>383 (45.4%)</td>
</tr>
</tbody>
</table>

**Table 2. Outcomes in PCI and CABG cohorts stratified by surgical risk**

**Conclusion:** Among low-risk STS patients, CABG seems to offer a significant benefit over PCI with respect to mortality, readmission, and repeat revascularization. While the benefits of CABG over PCI in the intermediate- and high-risk STS groups were not as statistically significant, this may be due to fewer patients in those groups; nonetheless, the trends all suggested a benefit with CABG. Future studies are needed reflecting routine practice to assess how best to approach shared-decision making and informed consent when it comes to revascularization decisions in patients with multivessel coronary artery disease.

**References:**


Presentation: Features Associated with Long-Term Survival in Metastatic Breast Cancer

Summary: Breast cancer (BC) is the second leading cause of cancer death among women in the United States. In 2018, 40,920 women are expected to die of this disease. Most of these deaths will be due to complications from metastatic breast cancer (MBC), also known as stage IV disease. MBC has a median survival of only 2 to 3 years. According to the latest SEER data (2008-2014), the 5-year survival rate for MBC is 27%. Known features associated with long-term MBC survival include hormone receptor-positive BC, and having non-visceral and bone metastases. Characteristics associated with short-term survival include triple-negative disease, having visceral metastases and having brain metastases. Data on factors associated with MBC survival are limited to analyses of large national databases from several countries including the United States, the Netherlands, Sweden, France and Australia. Many characteristics such as age, time interval between initial diagnosis and MBC diagnosis, and de novo MBC status have not been clearly shown to be linked to survival and have had mixed results between different studies. Since much of what is known of features associated with survival in MBC comes from analyses of large national databases, several variables which are not readily available in these databases have not yet been well investigated. Prior studies have limited and often lack data on socioeconomic variables as well as patients’ baseline comorbidities. In addition, there is ongoing debate regarding certain characteristics such as Her2-positive status, patient age, de novo MBC, and time interval between initial BC and MBC diagnosis and their associations with MBC survival. To address limitations in previous studies, we used data from patients seen at a large, urban breast cancer program in the United States to identify clinicopathologic and socioeconomic features associated with survival at the time of MBC diagnosis.

Methods: The current study is a retrospective analysis of a large breast cancer program in a cancer center in western Pennsylvania, United States. Women diagnosed with MBC in or after 1999 were included. In January 2018, we evaluated the database for long-term MBC survivors (greater than or equal to 5-year survival from date of MBC diagnosis) and short-term MBC survivors (less than or equal to 2-year survival from date from MBC diagnosis) and identified N=122 and N=191 subjects, respectively. Women included in the database (N=1425) who did not meet long-term or short-term survivor criteria were excluded. Differences between long-term and short-term MBC survivors were assessed using t-tests or Wilcoxon-
Mann-Whitney tests for continuous variables and Chi-square tests or Fisher’s exact tests for categorical variables. In addition, odds ratios (OR) and corresponding 95% confidence intervals (CI) for long-term survival were calculated using multivariate logistic regression models. All significance tests were two-sided; *P* values <0.05 were considered significant. All analyses were performed with use of the SAS® statistical software package (SAS version 9.4, SAS Institute Inc., Cary, NC).

**Results:** The study population included *N*=122 long-term MBC survivors and *N*=191 short-term MBC survivors. Selected characteristics are presented by survivor status in Table 1. In univariate analyses of the demographic variables (i.e., age at initial diagnosis, age at MBC diagnosis, time between initial and metastatic diagnosis, year of initial diagnosis, BMI, race, partner status, employment status, income status, and menopausal status), long-term survivors were significantly younger at initial BC diagnosis and at MBC diagnosis, more often partnered, had higher annual household income, and were more often premenopausal compared to short-term survivors. Long-term and short-term survivors differed significantly for year of initial diagnosis when taking all three groups into account (see Table 1). No significant differences were observed for BMI, race, and employment status. In univariate analyses of the clinico-pathologic variables (i.e., tumor receptor (ER, PR, Her2, triple-negative) status, de novo MBC, stage at initial diagnosis, tumor type, site of metastases, history of hypertension, and CCI) long-term survivors were significantly more often ER-positive, PR-positive, and Her2-positive at initial BC diagnosis and diagnosed with de novo MBC than short-term survivors. They also had significantly lower CCI and lower rates of visceral and brain metastases. Short-term survivors were significantly more often diagnosed with triple-negative initial BC compared to long-term survivors. No significant differences were observed for history of hypertension and initial BC tumor type (ductal, lobular, and other).

We subsequently conducted multivariate analyses to evaluate whether variables found to be significant in the univariate analyses remained significant after adjustment for potential confounding factors. Results are presented in Table 2 and below. Diagnosis of de novo MBC, premenopausal status, ER-positive status, and Her2-positive status remained significantly positively associated with long-term survival (respectively, OR: 2.68, 95% CI: 1.48-4.88; OR: 1.96, 95% CI: 1.02-3.79; OR: 3.74, 95% CI: 1.72-8.14; OR: 2.88, 95% CI: 1.61-5.14), while triple-negative status remained negatively associated with long-term survival (OR: 0.12, 95% CI: 0.05-0.29). Using the most commonly observed metastasis sites as reference group, i.e., bone with or without non-visceral metastases, having visceral plus bone metastases, and having brain metastases remained negatively associated with long-term survival (respectively, OR: 0.18, 95% CI: 0.07-0.47; OR: 0.16, 95% CI: 0.04-0.60). Age at initial BC diagnosis, age at MBC diagnosis, partner status, household income, CCI, and PR status were no longer significantly associated with survival in the multivariate analysis.

**Table 1: Clinical, Pathologic and Socioeconomic Characteristics of Long-term and Short-term Survivors**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Long-term survivors (<em>N</em>=122)</th>
<th>Short-term survivors (<em>N</em>=191)</th>
<th><em>P</em> value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial dx (yrs, mean±sd)</td>
<td>51.4±13.0</td>
<td>55.8±13.8</td>
<td>0.006</td>
</tr>
<tr>
<td>Age at metastatic dx (yrs, mean±sd)</td>
<td>53.2±12.7</td>
<td>57.8±13.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Overall survival (yrs, mean±sd)</td>
<td>9.8±3.4</td>
<td>3.0±2.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Survival after MBC dx (yrs, mean±sd)</td>
<td>8.0±2.5</td>
<td>1.0±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time between initial dx and MBC dx (mnths, mean± sd)</td>
<td>21.5±28.4</td>
<td>24.1±25.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Year initial diagnosis, N (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1999 - 2004</td>
<td>66 (54.1)</td>
<td>69 (36.1)</td>
<td></td>
</tr>
<tr>
<td>2005 - 2010</td>
<td>55 (45.1)</td>
<td>84 (44.0)</td>
<td></td>
</tr>
<tr>
<td>2011 - 2017</td>
<td>1 (0.8)</td>
<td>38 (19.9)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²; mean± sd)</td>
<td>28.4±6.4</td>
<td>30.0±7.5</td>
<td>0.11</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td>White</td>
<td>114 (93.4)</td>
<td>170 (90.9)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>8 (6.6)</td>
<td>17 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Partnered (yes), N (%)</td>
<td>85 (70.3)</td>
<td>110 (58.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Employed (yes), N (%)</td>
<td>55 (46.6)</td>
<td>79 (44.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Household income ($, mean±sd)</td>
<td>57,615±19,721</td>
<td>52,740±16,642</td>
<td>0.03</td>
</tr>
<tr>
<td>History of hypertension (yes), N (%)</td>
<td>36 (30.8)</td>
<td>62 (36.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Menopausal status, N (%)</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>54 (52.9)</td>
<td>61 (37.2)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>48 (47.1)</td>
<td>103 (62.8)</td>
<td></td>
</tr>
<tr>
<td>Charlson Comorbidity Index, N (%)</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>&lt;10</td>
<td>107 (93.4)</td>
<td>143 (83.6)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>8 (7.0)</td>
<td>28 (16.4)</td>
<td></td>
</tr>
<tr>
<td>ER-positive (yes), N (%)</td>
<td>94 (77.1)</td>
<td>101 (53.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PR-positive (yes), N (%)</td>
<td>72 (59.5)</td>
<td>73 (39.3)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Her2-positive (yes), N (%)</td>
<td>57 (50.0)</td>
<td>47 (24.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triple-negative (yes), N (%)</td>
<td>7 (5.8)</td>
<td>64 (33.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>De novo MBC (yes), N (%)</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>55 (48.3)</td>
<td>46 (24.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>59 (51.8)</td>
<td>140 (75.3)</td>
<td></td>
</tr>
<tr>
<td>Stage at initial dx, N (%)</td>
<td></td>
<td></td>
<td>0.0002</td>
</tr>
<tr>
<td>I</td>
<td>6 (5.3)</td>
<td>20 (10.8)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>32 (28.1)</td>
<td>61 (32.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>21 (18.4)</td>
<td>59 (31.7)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>55 (48.3)</td>
<td>46 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Type of breast cancer, N (%)</td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>Ductal</td>
<td>100 (84.8)</td>
<td>153 (87.9)</td>
<td></td>
</tr>
<tr>
<td>Lobular</td>
<td>14 (11.9)</td>
<td>14 (8.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (3.4)</td>
<td>7 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Site of metastases, N (%)</td>
<td></td>
<td></td>
<td>0.0007</td>
</tr>
<tr>
<td>visceral + bone +/- non-visceral</td>
<td>14 (11.6)</td>
<td>40 (20.9)</td>
<td></td>
</tr>
<tr>
<td>bone +/- non-visceral</td>
<td>51 (42.2)</td>
<td>43 (22.5)</td>
<td></td>
</tr>
<tr>
<td>non-visceral</td>
<td>21 (17.4)</td>
<td>33 (17.3)</td>
<td></td>
</tr>
<tr>
<td>visceral +/- non-visceral</td>
<td>31 (25.6)</td>
<td>53 (27.8)</td>
<td></td>
</tr>
<tr>
<td>brain +/- additional site</td>
<td>4 (3.3)</td>
<td>22 (11.5)</td>
<td></td>
</tr>
</tbody>
</table>

a Numbers do not always add up to the total number of short-term survivors or long-term survivors due to missing information.

b T-test or Wilcoxon-Mann-Whitney test for continuous and Chi-square test or Fisher’s exact test for categorical variables.
Table 2: Results from the multivariate analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>Adjusted for b:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial diagnosis</td>
<td>0.97</td>
<td>0.95-1.00</td>
<td>ER, PR and Her2 status, de novo and CCI</td>
</tr>
<tr>
<td>Age at diagnosis of metastases</td>
<td>0.97</td>
<td>0.95-1.00</td>
<td>ER, PR and Her2 status, de novo and CCI</td>
</tr>
<tr>
<td>Household income (above vs. below mean c)</td>
<td>1.37</td>
<td>0.77-2.41</td>
<td>Age, ER, PR and Her2 status, de novo and CCI</td>
</tr>
<tr>
<td>Partner status (yes vs. no)</td>
<td>1.38</td>
<td>0.74-2.58</td>
<td>Age, ER, PR and Her2 status, de novo and CCI</td>
</tr>
<tr>
<td>Menopausal status (pre vs. post)</td>
<td>1.96</td>
<td>1.02-3.79</td>
<td>ER, PR and Her2 status, de novo, and CCI</td>
</tr>
<tr>
<td>Charlson Comorbidity Index (≥10 vs. &lt;10)</td>
<td>0.37</td>
<td>0.12-1.16</td>
<td>Age, ER, PR and Her2 status, and de novo</td>
</tr>
<tr>
<td>ER-positive (positive vs. negative)</td>
<td>3.74</td>
<td>1.72-8.14</td>
<td>Age, PR and Her2 status, de novo, and CCI</td>
</tr>
<tr>
<td>PR-positive (positive vs. negative)</td>
<td>1.11</td>
<td>0.55-2.26</td>
<td>Age, ER and Her2 status, de novo, and CCI</td>
</tr>
<tr>
<td>Her2-positive (positive vs. negative)</td>
<td>2.88</td>
<td>1.61-5.14</td>
<td>Age, ER and PR status, de novo, and CCI</td>
</tr>
<tr>
<td>Triple-negative (yes vs. no)</td>
<td>0.12</td>
<td>0.05-0.29</td>
<td>Age, de novo, and CCI</td>
</tr>
<tr>
<td>De novo MBC (yes vs. no)</td>
<td>2.68</td>
<td>1.48-4.88</td>
<td>Age, ER, PR and Her2 status, and CCI</td>
</tr>
<tr>
<td>Site of metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bone +/- non-visceral</td>
<td>1.0</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>visceral +/- non-visceral</td>
<td>0.18</td>
<td>0.07-0.47</td>
<td></td>
</tr>
<tr>
<td>non-visceral</td>
<td>0.68</td>
<td>0.28-1.69</td>
<td></td>
</tr>
<tr>
<td>visceral +/- non-visceral</td>
<td>0.88</td>
<td>0.40-1.87</td>
<td></td>
</tr>
<tr>
<td>brain +/- additional site</td>
<td>0.16</td>
<td>0.04-0.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age, ER, PR and Her2 status, de novo, and CCI</td>
</tr>
</tbody>
</table>

a Long-term survivors were compared to short-term survivors. That is, the odds of being a long-term survivor is shown.
b Age is age at MBC diagnosis (continuous); ER status (positive, negative); PR status (positive, negative); Her2 status (positive, negative); CCI (≥10 vs. <10); and de novo (yes, no).
c Used mean annual household income of the total study population ($54,636)

Conclusions: This study aimed to find which clinico-pathologic and socioeconomic features were associated with survival in MBC. This study is one of the first to show that de novo MBC and premenopausal status are associated with survival in MBC after adjustment for potential confounders. In addition, this study found that both ER-positive and Her2-positive status were associated with increased survival and that triple-negative status was associated with decreased survival. Brain metastases and visceral plus bone metastases were associated with worse survival. This study also showed an association with income and partner status with survival in the univariate analyses. These findings can easily be applied to clinical practice to help predict the length of survival at MBC diagnosis. More studies, including large multicenter prospective cohort analyses are needed to confirm our results regarding the survival benefit de novo MBC confers. Future research investigating genomic and immunologic differences as well as social determinants of health among MBC patients will help to further elucidate additional features associated with survival.

References:


Oral Presenter – April 29, 2019

Daniel Kotok, MD

PGY-2 Resident – Clinical Research

Bio: Daniel is a second-year Internal Medicine resident at the UPMC McKeesport program with a passion for pulmonary and critical care medicine, planning to pursue a career as an academic pulmonologist-intensivist. He was born and raised in Jerusalem, Israel and moved to Pittsburgh for his residency in 2017. Early in his intern year, he became involved in clinical/translational research under the mentorship of Dr. Georgios Kitsios and Dr. Bryan McVerry from the Division of Pulmonary, Allergy and Critical Care Medicine. He is actively working on several projects in the fields of ARDS and sepsis. In his free time, he enjoys the company of his friends, running, playing his guitar(s) and coding in Python and R.

Presentation: Plasma \(\beta\)-d-glucan levels are associated with host inflammation and injury and clinical outcomes in mechanically-ventilated adult patients.

Summary: Measurement of the fungal cell wall constituent \((1,3)\)-\(\beta\)-d-glucan (BDG) is recommended for diagnosis of invasive fungal infections (IFI), but detectable systemic levels may also occur from gut translocation of fungi in the absence of infection. The clinical importance of systemic BDG levels in critically-ill patients without evidence of IFI has not been established. We thus examined associations between BDG levels with clinical outcomes and host-response biomarkers in a cohort of mechanically-ventilated patients.

Methods: We enrolled consecutive patients with acute respiratory failure from the University of Pittsburgh Acute Lung Injury Registry and Biospecimen Repository and obtained plasma samples within 48hrs of intubation. We classified BDG levels (Fungitell assay, Associates of Cape Cod) as negative (\(\leq 60\) pg/ml) or positive (\(>60\) pg/ml) based on established thresholds for IFI. We measured plasma biomarkers (Luminex assay) of host epithelial injury (Receptor for Advanced Glycation End-products [RAGE]), endothelial injury (Angiopoetin-2), inflammation (Interleukin-6 [IL-6], IL-8 and soluble tumor necrosis factor receptor-1 [sTNFR1]) and bacterial infection (procalcitonin). We classified patients into hyper-inflammatory vs. hypo-inflammatory subphenotype based on a published logistic regression model using IL-8, sTNFR1 and bicarbonate levels.

Results: 220 patients (median age 59.5 years, 49% women, 25% with acute respiratory distress syndrome) were included. No patient had culture-proven fungemia. Patients with positive BDG levels (\(n=43, 20\%\)) had similar sequential organ failure scores, degree of hypoxemia, incidence of shock and bacteremia compared to patients with negative BDG results (Table 1). However, patients with elevated BDG levels had fewer ventilator-free days (median 16 vs. 21, \(p<0.01\)) and higher 30-day mortality risk (44% vs. 19%, \(p<0.01\)). Furthermore, positive BDG results were significantly associated with higher levels of individual host-response biomarkers (\(p\)-values <0.05) and assignment to the hyper-inflammatory subphenotype (59% vs 21%, \(p=0.003\)) that has been associated with poor prognosis. Similar results were obtained in sensitivity analyses with a higher threshold (\(>80\) pg/ml) for BDG positivity.
Table 1. Baseline characteristics and clinical outcomes in mechanically-ventilated patients stratified by BDG test results. P-values from nonparametric tests are shown in bold when significant (p < 0.05). BMI: Body mass index; P:F Ratio: Ratio of partial pressure of arterial oxygen and fraction of inspired oxygen; SOFA Score: Sequential organ failure assessment score; VFD: ventilator free days.

<table>
<thead>
<tr>
<th>Variable Name / BDG Category</th>
<th>Negative</th>
<th>Non-negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>177</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>91 (51.4)</td>
<td>22 (51.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Age (median [IQR])</td>
<td>59.35 [45.98, 68.52]</td>
<td>60.29 [41.80, 66.20]</td>
<td>0.749</td>
</tr>
<tr>
<td>BMI (median [IQR])</td>
<td>30.35 [25.47, 37.56]</td>
<td>27.61 [25.02, 32.76]</td>
<td><strong>0.028</strong></td>
</tr>
<tr>
<td>Vasopressor Requirement (%)</td>
<td>80 (45.2)</td>
<td>26 (60.5)</td>
<td>0.104</td>
</tr>
<tr>
<td>Bacteremia (%)</td>
<td>19 (10.7)</td>
<td>6 (14.0)</td>
<td>0.742</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>98 (55.4)</td>
<td>24 (55.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>SOFA Score (median [IQR])</td>
<td>6.00 [4.00, 8.00]</td>
<td>7.00 [4.00, 10.00]</td>
<td>0.062</td>
</tr>
<tr>
<td>P:F Ratio (median [IQR])</td>
<td>164.00 [117.00, 205.00]</td>
<td>168.00 [123.50, 235.50]</td>
<td>0.624</td>
</tr>
<tr>
<td>VFD (median [IQR])</td>
<td>21.00 [12.00, 24.00]</td>
<td>16.00 [0.00, 22.00]</td>
<td><strong>0.007</strong></td>
</tr>
<tr>
<td>30 Day Mortality (%)</td>
<td>34 (19.2)</td>
<td>19 (44.2)</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>90 Day Mortality (%)</td>
<td>38 (21.5)</td>
<td>19 (44.2)</td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>

Figure 1. Linear associations between plasma BDG levels and biomarkers of acute inflammation and injury. Statistically significant associations are denoted by the red square indicating the degree of correlation using Pearson’s correlation. IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; TNFR-1: Tumor necrosis factor receptor-1; Ang-2: Angiopoietin-2; ST-2: Suppression of tumorogenicity-2; RAGE: Receptor for advanced glycation end-products.
Conclusions: In unselected patients with acute respiratory failure and no culture evidence of fungemia, a positive baseline BDG assay was strongly associated with host-response biomarkers of injury and inflammation and worse patient-centered outcomes. In the absence of evidence of IFI, our findings are hypothesis-generating for the possibility that subclinical, fungal translocation in critically-ill patients may lead to host inflammation and adverse clinical outcomes. Further study of BDG measurements adjusted for potential confounders with parallel interrogations of the mycobiome and intestinal permeability in critical illness is warranted.
Oral Presenter – April 30, 2019
Marta Bueno, PhD

Research Assistant Professor of Medicine – Bench (Basic Science) Research

Bio: Marta Bueno is a junior faculty in the Aging Institute and the Division of Pulmonary and Critical Care Medicine. She received her Ph.D. in Biochemistry from the University of Zaragoza, Spain. Her work, a collaboration between the Department of Computational and System Biology and the Division of Transplant Pathology, on advanced computational drug discovery techniques and the development of new antiviral compounds for kidney transplant patients, earned Dr. Bueno a Thomas E. Starzl Postdoctoral Fellowship in Transplantation Biology. She joined the Vascular Medicine Institute under the mentorship of Dr. Ana Mora. Her research focus on understanding the mechanisms involved in the increased vulnerability of the aging lung to develop lung fibrosis and other diseases characterized by abnormal tissue repair and exaggerated remodeling, including pulmonary hypertension. Since summer, Dr Bueno is now part of the Aging Institute at Brigdeside Point.

Presentation: Cyb5R3 in alveolar epithelial cells confers protection against the development of lung fibrosis through suppression of TGF-β signaling

Summary: Alterations in the redox homeostasis play a role in the pathogenesis of age-related diseases such as idiopathic pulmonary fibrosis (IPF). The most accepted theory in the pathogenesis of IPF is the injury and activation of alveolar epithelial type II cells (AECII) triggering excessive and chronic wound-healing responses, mediated by growth factors such as TGF-β. A mitochondrial membrane-bound NADH-dependent redox enzyme that contributes to stress protection and associates with healthspan and aging is cytochrome b5 reductase isoform 3 (Cyb5R3). However, the link between Cyb5R3 expression levels in AECII with the modulation of the TGF-β signaling pathways and the age-related vulnerability to injury and fibrosis in the lung is unknown.

Methods: Lungs from young, old and IPF donors were lysated to test Cyb5R3 levels. Cyb5R3 flox mice (Cyb5R3 fl/fl or WT) and mice carrying a doxycycline-inducible Cre-recombinase under the control of a regulatory sequence of the SP-C gene were bred. To promote recombination and generate a homozygous conditional type II lung epithelial cells (AECII) CYB5R3 knockout mice (AECII Cyb5R3 KO), mice were fed doxycycline chow (625 mg/kg, Envigo) for 2 weeks before injury or AECII isolation (Fig. 1a). Mice were infected intranasally with gammaherpesvirus 68 (MHV68) to evaluate inflammatory and fibrotic responses in the lung. Mouse alveolar epithelial cell line MLE12 was used to knockdown Cyb5R3 using adenovirus carrying scramble shRNA or Cyb5R3 shRNA constructs (Fig. 1b).
Results: We analyzed the expression of Cyb5R3 in the human lung. Aged donor and IPF total lung lysates show lower levels of Cyb5R3 (Fig. 2a). In addition, isolated murine primary AECII showed that Cyb5R3 is significantly diminished in aging AECIIs when compared to young controls (Fig. 2b).

To explore the potential role of Cyb5R3 on epithelial injury and fibrosis in vivo, we subjected Cyb5R3fl/fl (Cyb5R3 WT) and AECII Cyb5R3 KO littermate mice to our model of lung fibrosis by infection with the murine gammaherpesvirus 68 (MHV68). Analysis of lung pathology of Cyb5R3 WT infected mice showed limited interstitial pneumonia and vasculitis in contrasts to AECII Cyb5R3 KO mice that develop extended areas of interstitial fibrosis (Fig. 2c), which correlated with higher collagen deposition and significant higher transcript levels of TIMP1 (tissue inhibitor of the MMPs) and osteopontin.

Since TGF-β is a key modulator of the net balance between MMPs and TIMPs, we analyzed the role of Cyb5R3 in TGF-β signaling. To analyze if Cyb5R3 modulates TGF-β downstream signaling pathway, we used MLE cells treated with Cyb5R3shRNA and scramble control. Analysis of transcript levels of osteopontin showed increased levels after TGF-β treatment that was further enhanced by depletion of Cyb5R3 (Fig. 2d). In addition, deficiency of Cyb5R3 enhances TGF-β signaling by modulation of cGMP-PKG and cAMP-PKA pathways.

Figure 1. Confirmation of Cyb5R3 deletion in the AECII Cyb5R3 KO mice (A) and in MLE12 cells (B).

Figure 2. (A) Low expression of Cyb5R3 in total IPF lungs analyzed by mRNA transcript and protein levels (†p<0.001 vs. young; n=5). (B) Lower Cyb5R3 transcript levels in AECII isolated from old (24 months old) C57BL6J mice compared with younger (4 months old) counterparts (***p<0.001 vs. young, n=3; unpaired t test). (C) Representative Masson trichrome staining in lung sections showing increased collagen deposition (blue) at 15 days post infection (15dpi) in AECII Cyb5R3 KO. (D) Analysis of transcript levels of osteopontin showed increased levels after TGF-β treatment that was further enhanced by Cyb5R3 knockdown (*p<0.0001 as indicated, n=6).
Conclusions: Altogether, these data suggest a possible role for Cyb5R3 in the regulation of the profibrotic TGF-β signaling pathway in the AECII and the age related susceptibility to lung fibrosis. Strategies designed to modulate Cyb5R3 expression or function in the lung might lessen severity of pulmonary fibrosis, especially in the context of the aging lung.
Oral Presenter – April 30, 2019

Aravind Cherukuri, MD, PhD

Clinical Fellow – Translational Research

Bio: Aravind Cherukuri is a first year Clinical Fellow in the division of Nephrology at UPMC. Aravind graduated from Medical School in India in 2000. Then, he immigrated to the UK to pursue postgraduate training in Internal Medicine. He completed his residency in Internal Medicine at Monklands Hospital in Airdrie, in Scotland after which he moved to Leeds in England to train as a Nephrology Fellow at St. James’s University Hospital, where he was attracted to the field of Transplantation. With the encouragement of his mentor Dr. Richard Baker, he developed a translational research project centered around the role of human B cells in renal transplant rejection that led to the completion of the thesis titled: The diverse roles of B lymphocytes in human renal transplantation and an award of PhD from the University of Leeds. After the completion of his clinical and research training in Leeds, he moved to the Pittsburgh to work as a post-doctoral research fellow under the mentorship of Dr. David Rothstein where he spearheaded a large translational prospective study to examine cytokine expressing B lymphocyte subsets and their ability to predict and prognosticate renal transplant outcomes. Outside Nephrology and Transplantation, Aravind enjoys cooking and reading non-fiction.

Presentation: Prospective Multicenter Validation of Human Transitional B Cell Cytokines as a Predictive Biomarker in Renal Transplantation

Summary: Despite 1-year graft survival of ~93%, long-term renal allograft survival rates have not improved over time. Allograft loss after the first year is frequently due to the cumulative effects of immunological rejection that is not clinically apparent until irreversible damage has already occurred. Such patients return to the waiting list, exacerbate the organ shortage, and have high mortality rates. Thus, prolonging long-term renal allograft survival is major unmet need. There is an acute need for non-invasive biomarkers that can identify patients at high risk for subsequent immunological damage, allowing for a pre-emptive increase in immunosuppression before allograft damage and further immune system activation have occurred.

Regulatory and effector B cells can either promote or inhibit inflammatory T cell responses, respectively, through the elaboration of inhibitory or inflammatory cytokines. These “Breg” and “Beff” cells can dramatically alter immune responses to infection, autoimmunity and alloimmunity. We discovered that Breg activity correlates best with the ratio of IL-10:TNF-a in various B cell subsets, and these two cytokines augment and inhibit Breg activity, respectively. In this prospective multicenter study, we assessed B cell subsets and their cytokine expression for the analysis of IL-10/TNF-a ratio to serve as a predictive biomarker.

Methods: Human Lymphocytes were isolated from serial blood samples in patients transplanted at UPMC between 2013 and 2015. Briefly these lymphocytes were stimulated for 24hrs with CD40L expressing NIH 3T3 Cell line along with Cpg ODN 2006. B cells were then stained and analyzed for the expression of IL-10 and TNF-α by flowcytometry. Of the lymphocyte subsets, the most immature T-1 transitional B cells (T1 TrBs) demonstrated the highest IL-10/TNF-α expression and exhibited invitro regulatory activity (Fig 1). The cytokine profiles of these cells were examined to perform as an early biomarker of clinical course.
**Fig 1: Human Transitional B cells (TrBs) and IL-10/TNF-α cytokine expression ratio**

The top panel shows the scatter plots to identify TrB subsets (from CD19+ B cells) and the bar chart compares IL-10/TNF-α ratio amongst various B subsets

**Results:** 165 patients (transplanted in 2013-14) with serial biopsies (Bxs) (including 3&12mo protocol Bxs + for-cause Bxs) and serial blood draws (0, 1, 3, 6 & 12mos) served as the training set. Immunosuppression utilized Thymoglobulin induction followed by mycophenolate and tacrolimus maintenance. A low T1B IL10:TNF-α ratio at 3mo predicted acute rejection (AR) within the 1st yr (Fig 2). Notably, in patients with a normal Bx at 2-4mo, a low T1B cytokine ratio strongly predicted late AR (6-12mo; AUC 0.9, p<0.0001) with a lead time of > 7mo in 80% of the patients. These data were validated in an independent internal cohort (2015, n=92). Further, a low T1B cytokine ratio was associated with IFTA (12 mos) and graft loss/impending graft loss (eGFR<30ml/min & >30% fall from baseline) at 4yrs. The predictive value of this biomarker was not influenced by either opportunistic viral infections or by non-adherence.

**Fig 2: T1 TrB IL-10/TNF-α ratio in patients with no rejection within the 1st year post-transplant (NR) vs. those with acute rejection (AR).** ROC- AUC demonstrating the strength of this association
Next, T1B cytokine ratio was validated in an external cohort (n=98) from the UK. Immunosuppression utilized Basiliximab induction followed by TAC+MMF maintenance. As protocol Bxs were not performed in this cohort, all AR was clinical. Again, the T1B cytokine ratio at 3mo strongly predicted AR within the 1st yr (Fig 3) and was associated with significantly greater graft loss/impending graft loss.

Fig 3: ROC - AUC for T1 TrB IL-10/TNF-a ratio in the external validation set (n=98)

B cells in high-risk patients express excessive TNFα relative to IL-10. Culture of B cells from such patients with α-TNF, reduced their TNFα and increased their IL10 expression. Such B cells subsequently suppressed autologous α-CD3 stimulated T cell TNFα while increasing IL10 expression. Thus, TNF blockade restored a normal B cell cytokine balance and their Breg activity in high-risk patients. Finally, α-TNF inhibited in vitro differentiation of B cells to plasma cells, reduced their Ab secretion, and selectively increased their IL-10 expression. These data provide rationale for the potential use of anti-TNF to restore Bregs in high risk renal transplant recipients.

Conclusion: Thus, T1B IL10:TNFα ratio (2-4 mo) was tested and validated as a strong biomarker for subsequent renal allograft rejection and clinical course. Importantly, our data not only identifies patients in need of pre-emptive therapy, but also provides rationale for therapeutic intervention based on TNF blockade.
Elise Martin, MD, MS

Junior Faculty – Quality Improvement Research

Bio: Elise Martin, MD, MS is an Assistant Professor in the Department of Medicine in the Division of Infectious Diseases. Dr. Martin attended Georgetown University School of Medicine and completed internship and residency in Internal Medicine at UCLA. She completed an Infectious Diseases fellowship at UCLA Health and received a Master’s in Clinical Research during her fellowship. Dr. Martin is the Associate Medical Director of Infection Prevention and Hospital Epidemiology at UPMC Presbyterian. She is interested in quality improvement research in infection prevention, especially how we use personal protective equipment and contact precautions to decrease the spread of infections, while trying to maintain high quality patient care.

Presentation: No Increase in MRSA or VRE Healthcare-Associated Infections After Discontinuing Routine Contact Precautions in a Large Health System

Summary: Given data on patient harms associated with contact precautions and limited data on efficacy, some institutions have discontinued routine contact precautions for methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococcus (VRE) without increasing healthcare-associated infections (HAI), but this is largely limited to uncontrolled single-center studies. The purpose of this study was to determine the impact of discontinuing contact precautions on HAIs across a large health system with control hospitals.

Methods: Routine contact precautions for MRSA and VRE were discontinued in 12 hospitals (bed size range 40-495) on 2/15/18 and continued at 3 control hospitals (bed size range 315-745). This was a system-wide decision, including community and tertiary hospitals within the UPMC system, and hospitals were independently able to assess their readiness for changing policy. Three hospitals decided not to change policy. Each hospital collected routine surveillance data for public reporting based on National Healthcare Safety Network (NHSN) definitions. These data on MRSA and VRE HAI from 1/2017 to 9/2018 and MRSA LabID events from 3/2017 to 9/2018 were collected directly from NHSN. Pre/post data from each institution and aggregated data were analyzed by Poisson regression and compared to controls; 2/2018 was excluded as a wash-in period. Cost analysis was performed on aggregated monthly purchasing of contact precautions gowns before and after the policy change to assess the financial impact.

Results: Aggregated average HAI rates before and after discontinuing contact precautions were 0.14 and 0.15 MRSA HAI/1000 patient days, 0.06 and 0.04 VRE HAI/1000 patient days, and 0.04 and 0.03 MRSA LabID events/100 admissions (Figure 1). There was no statistically significant increase in these rates after the change or when compared to control hospitals (Table 1). None of the hospitals that discontinued precautions had a statistically significant increase in MRSA or VRE HAI rates, and only one had MRSA LabID rate increase (pre 0.04, post 0.11, p-value 0.009). Average monthly aggregated spending on contact precautions decreased from $53,655 to $22,430, which is a projected cost savings of $374,696 over 1 year.
Figure 1: MRSA and VRE HAI rates in the pre and post periods in aggregated intervention and control hospitals.

Table 1: GEE Poisson Models Comparing Contact Precaution Change

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<td>0.04</td>
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*Rate and 95% Confidence interval
DC = Discontinuation

*Rate and 95% Confidence interval
DC = Discontinuation
**Conclusions:** Discontinuing contact precautions for MRSA/VRE lead to a significant cost savings on contact precautions gowns and did not result in increased rates of MRSA or VRE HAIs after seven months. While these are encouraging initial findings, further data are necessary on the optimal hospital conditions necessary to make this policy change successful.

**References:**
Oral Presenter – April 30, 2019

Thomas Radomski, MD, MS

Assistant Professor of Medicine – Health Services Research

Bio: Dr. Radomski is an Assistant Professor of Medicine and Clinical & Translational Science within the Division of General Internal Medicine. He is also affiliated with the Center for Pharmaceutical Policy & Prescribing and the VA Center for Health Equity Research and Promotion. He received his MD degree from the Penn State College of Medicine and completed his Internal Medicine Residency and Chief Resident Year at the University of Pittsburgh Medical Center. He stayed at Pitt for his General Internal Medicine Fellowship, during which time he was supported by a National Research Service Award and earned his Master’s Degree in Clinical Research. Dr. Radomski is currently a NIH KL2 Scholar. His research focuses on ways to accurately measure and reduce the provision of low-value care and how the receipt of care across multiple healthcare systems influences health service utilization, outcomes, and value. In addition to conducting research, Dr. Radomski is a practicing general internist in both the inpatient and outpatient settings and is the President of the Society of General Internal Medicine Mid-Atlantic Region.

Presentation: Low-Value Prostate Cancer Screening within the Veterans Health Administration

Summary: Prostate specific antigen (PSA) screening for prostate cancer is of low value in men with a limited lifespan. Because most patients managed in the Veterans Health Administration (VA) are older males, low-value PSA screening in VA is likely to be common, exposing Veterans to excessive costs and unnecessary health risks. Our objective was to quantify the frequency and variation of low-value PSA screening across VA Medical Centers (VAMCs).

Methods: We examined a national 20% random sample of Veterans aged ≥75 using VA data from fiscal years (FY) 2014–2015. Using a claims-based algorithm, we defined low-value PSA screening as screening among men aged ≥75 without a history of prostate cancer. We calculated rates of low-value PSA screening in FY15 by VAMC, adjusting for sociodemographic and VAMC-level factors. We characterized variation across VAMCs using the adjusted median odds ratio (OR). We also divided VAMCs into deciles of low-value PSA screening and calculated the adjusted OR of undergoing low-value screening for Veterans within each decile. To increase the specificity of our claims-based algorithm, we determined low-value PSA screening rates after excluding Veterans who underwent prostatectomy, had a prior PSA elevation, or had a clinical reason for PSA testing, such as hematuria. In subgroup analyses, we assessed low-value PSA screening rates in Veterans at greatest risk of mortality based on a Gagne Comorbidity Index Score ≥ 3.

Results: Among 214,480 Veterans aged ≥75 who received care in 127 VAMCs, 37,866 (17.7%) received low-value PSA screening, with adjusted VAMC rates ranging from 3.3%-38.2% (Figure 1). The adjusted median OR was 1.88, meaning the median odds of receiving low-value PSA screening would increase by 88% were a Veteran to transfer his care to a VAMC with more low-value testing. Veterans at VAMCs in the top decile had an adjusted OR for receiving low-value PSA screening of 12.9 (CI 11.0–15.2) compared to those in the lowest decile (Table 1). After excluding Veterans with a prior prostatectomy, PSA elevation, or acute symptoms, 31,556 (14.7%) received a low-value PSA test, ranging from 2.0%-49.9% across VAMCs. Among Veterans with the greatest comorbidity burden (n=23,377), 3,496 (15.0%) received a low-value PSA screening test (1.7%-46.3% across VAMCs).
**Conclusions:** In a national cohort of older Veterans, more than 1 in 6 received low-value PSA screening, with greater than 10-fold variation across VAMCs. The frequency of low value PSA screening remained high even among Veterans without a clinical indication for testing and in those with the clearest limit to life expectancy. Our findings suggest that even in a national integrated health system with robust decision support tools for ordering tests, low-value care among older adults remains challenging to address. These findings also highlight the need to accurately identify and accounting for unique VAMC-level factors when developing interventions to mitigate the provision of low-value care.

**Figure 1:** Adjusted Rates of Low-value PSA Screening Across 127 VA Medical Centers Stratified by Geographic Region in Fiscal Year 2015

- Bar color depicts United States Census Regions. (Black: Midwest, Red: Northeast, Green: South, Blue: West)
- Error bars represent 95% confidence intervals for adjusted rates of PSA testing (i.e., men aged ≥75 without a history of prostate cancer who received a PSA test).
- PSA rates adjusted for the following patient-level and VAMC-level factors: Patient-level factors (FY2014): age, race/ethnicity, marital status, VA priority group at the time of enrollment, travel time to the nearest VAMC and Gagne Comorbidity Score. VAMC factors: academic affiliation, facility size (depicted by number of outpatient visits in FY14), VAMC complexity rating, and US Census region location.
- Abbreviations: PSA = Prostate Specific Antigen, VAMC = Veterans Affairs Medical Center
### Table 1: Adjusted Odds Ratio of Undergoing Low-Value Prostate Specific Antigen Screening in Fiscal Year 2015 by VA Medical Center Decile

<table>
<thead>
<tr>
<th>Decile</th>
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<th>Sensitivity Analysis</th>
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<tr>
<td></td>
<td>PSA Rate (%)</td>
<td>Adjusted Odds Ratio (95% CI)</td>
<td>PSA Rate (%)</td>
<td>Adjusted Odds Ratio (95% CI)</td>
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<td>1</td>
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<td>4.0</td>
<td>Reference level</td>
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<tr>
<td>2</td>
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<td>1.9 (1.6, 2.2)</td>
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<td>3</td>
<td>11.5</td>
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<td>12.9 (11.0, 15.2)</td>
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</table>

a. Primary analysis: incorporates men aged ≥75 without a history of prostate cancer.
b. Sensitivity analysis: incorporates men aged ≥75 without a history of prostate cancer, who did not undergo prostatectomy, have a prior PSA elevation, or have an acute reason for PSA testing as depicted in ICD-9 codes.
c. PSA rates depict the unadjusted mean rates of VAMCs within the corresponding decile.
d. Odds ratios adjusted for the following patient-level and VAMC-level factors Patient-level factors (FY2014): age, race/ethnicity, marital status, VA priority group at the time of enrollment, travel time to the nearest VAMC and Gagne Comorbidity Score. VAMC factors: VAMC where each Veteran receives the majority of their outpatient care, academic affiliation, facility size (depicted by number of outpatient visits in FY14), VAMC complexity rating, and Census Region Location.
e. Abbreviations: PSA = Prostate Specific Antigen, VAMC = VA Medical Center
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**Poster: Impact of Beta Agonist Exposure on Macrophage Immunometabolism**

**Presenter:** Kristin Berger, Resident

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Nathaniel Weathington MD/PhD

**Authors:** Kristin Berger MD, Nathaniel Weathington MD/PhD

**Introduction:** In response to infection, macrophages reprogram their cellular metabolism to generate large quantities of ATP through glycolysis. Intense beta agonist therapy suppresses the cyclic AMP signaling pathway in macrophages needed for glycolytic activation. Severe asthmatics are prescribed long-acting high dose beta agonist therapy, which has implications for macrophage immunometabolism. Suppression of glycolytic metabolism in macrophages could alter their immune effector functioning. Essential cellular factors implicated in glycolytic switching of macrophages include the hypoxia inducible factor 1a (HIF1α) and the mechanistic target of rapamycin (mTOR). We evaluated the impact of beta agonist exposure on monocytic THP1 cells and alveolar macrophages in terms of glycolytic induction, phagocytosis, response to bacterial challenge, and activity of HIF1α and mTOR.

**Methods:** THP1 monocytes or primary macrophages from mice and humans were exposed to beta agonist isoproterenol acutely (1h) or for prolonged periods (24h) and also exposed to inflammatory stimuli including LPS. Seahorse XF Analyzer was used to measure glycolysis within cells by the extracellular acidification rate (ECAR). Cellular phagocytosis and bacterial killing assays were performed with the fluorescent pHrodo probe or bacterial challenge respectively, with quantitation of fluorescence or colony forming units as measures of effector function. HIF1α abundance was evaluated with immunoblotting and quantitative RT-PCR. mTOR activity and function was assessed by immunoblot for phosphorylation of the S6 target of activated mTOR and by addition of the inhibitor rapamycin.

**Results:** THP1 cells exposed to LPS demonstrated robust glycolytic response as measured by ECAR compared to LPS unexposed conditions. Prolonged isoproterenol exposure suppressed glycolysis in THP cells at rest, and prevented glycolytic induction by LPS exposure. Cells treated with prolonged beta agonist also demonstrated less robust phagocytosis of pHrodo bacterial bioparticles and deficient early killing of S. aureus and E. coli bacteria. Transcript levels of HIF1α were reduced in human asthmatic patient BAL samples relative to healthy controls and in correlation with intensity of beta agonist use. mTOR activity was significantly induced by acute, but suppressed by prolonged isoproterenol treatment. Rapamycin suppressed glycolysis independently of isoproterenol.

**Conclusion:** Beta agonists are the most commonly prescribed drugs for patients with airway disease. Intense beta agonist therapy exposure was demonstrated to alter monocyte cellular metabolism, resulting in suppression of glycolytic metabolism and effector function in response to bacterial challenge. This effect may in part be driven through beta agonist-mediated modulation of metabolic regulators HIF1α and mTOR.
Introduction: The pathophysiology underlying the development of diastolic dysfunction remains complicated and poorly understood. A number of molecular mechanisms have been implicated in the disease process, including: increased interstitial fibrosis, increased oxidative damage, increased myocyte stiffness, altered calcium handling and mitochondrial dysfunction. Mitochondrial dysfunction has been associated with the accumulation of mitochondrial DNA damage and depressed mitophagy, resulting in altered energetics and worsening reactive oxygen species production. We hypothesized that mitochondrial dysregulation is the primary mechanism driving early diastolic dysfunction. Using an angiotensin-II infusion, we developed a mouse model of hypertension-related early diastolic dysfunction. However, we found no evidence of mitochondrial pathology despite clear evidence of diastolic disease.

Methods: 8-week old C57BL/6 mice were implanted with high-dose angiotensin pumps (1000 ng/kg/min) for four weeks. Baseline and four-week transthoracic echocardiographic images were obtained using both Vevo 770 and Vevo 3100 imaging systems. Systolic and diastolic dysfunction were evaluated using traditional b-mode and doppler modalities as well as strain analysis via speckle tracing. Non-invasive tail-cuff blood pressures were measured prior to sacking. Hearts were flash frozen or formalin fixed and analyzed via Western blot, qPCR, digital PCR, histology, and electron microscopy for markers of mitochondrial damage.

Results: Following four weeks of angiotensin-II treatment, mice had significantly elevated blood pressure compared to untreated littermates. Angiotensin-II treated mice had evidence of mild hypertrophy based on echocardiographic and histologic measurements but had no evidence of systolic dysfunction. Treated mice had slowed isovolumic relaxation time and decreased radial strain rate, consistent with diastolic dysfunction. However, Angiotensin-II treated mice had no changes to electron transport chain protein expression, markers of mitophagy (LC-3), or mitochondrial transcription factor A (TFAM). Treated mice had no changes to total mitochondrial DNA copy number via qPCR or mitochondrial DNA damage via digital PCR when compared to untreated mice. Visualization the mitochondria by electron microscopy found no changes to mitochondrial size, density, or circularity between groups.

Conclusion: We hypothesized that mitochondrial dysfunction was the earliest molecular mechanism underlying diastolic dysfunction. However, we found no evidence of mitochondrial pathology in an angiotensin-induced mouse model of early diastolic dysfunction. This finding contradicts current models that have implicated mitochondrial protein and genetic changes as a critical driver of diastolic dysfunction.
3-R Poster: Performance of Laboratory-Based Noninvasive Fibrosis Tests in Severely Obese Patients with NAFLD

Presenter: Joud Arnouk, Resident

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Jaideep Behari PhD

Authors: Joud Arnouk MD, Diana Marie Jaiyeola MD, vikrant Rachakonda MD, Jaideep Behari PhD

Introduction: Obesity is the primary risk factor for nonalcoholic fatty liver disease, and the prevalence of extreme obesity (defined as BMI > 50) is rising rapidly worldwide. There is limited understanding regarding effectiveness of noninvasive measures of fibrosis in this population. The aim of the study is To determine the diagnostic performance of commonly used laboratory based, noninvasive fibrosis tests in patients with NAFLD and extreme obesity.

Methods: This study was approved by the IRB at University of Pittsburgh. We identified 125 patients with BMI > 50 who underwent liver biopsy that demonstrated histologic evidence of NAFLD. We recorded demographic and clinical data at the time of liver biopsy to calculate the Bard Score, Fibrosis-4 (FIB-4), AST-to-platelet ratio index (APRI), and NAFLD Fibrosis Score (NFS). We then performed receiver operator curve analysis to assess the accuracy of these scoring systems for identification of advanced fibrosis, defined as Metavir F3 or F4 fibrosis. Categorical variables were compared using Fisher’s exact tests, and continuous variables were compared using Welch’s t tests.

Results: Out of 125 patients, 79 (63.2%) had advanced fibrosis, and subjects with advanced fibrosis were older [58.4(56.0-60.8) yr vs 52.7(49.0-56.5) yr, p=0.0046], while BMI and gender distribution did not difference between groups with advanced and non-advanced fibrosis. Diabetes mellitus [47 (56.9%) vs 11 (23.9%)] and dyslipidemia [46 (58.2%) vs 18 (39.1%)] were more common in subjects with advanced fibrosis. Platelet count and albumin were lower, while bilirubin was higher in patients with advanced fibrosis. In multivariable logistic models, only presence of diabetes [HR 3.351 (95% CI 1.259-8.916), p=0.015] and platelet count [HR 0.993 (0.987-0.999), p=0.040] were significantly associated with advanced fibrosis. Using ROC curves, we found no significant differences between all 4 scoring systems for identification of advanced fibrosis [FIB-4: AUROC 0.7874 (95% CI 0.7006-0.8742), NFS: 0.7747 (0.6885-0.8609), APRI 0.7873 (0.6985-0.8761), Bard: 0.6755 (0.5781-0.7728, p=0.1196 between groups).

Conclusion: In patients with NAFLD with BMI > 50, laboratory-based noninvasive fibrosis tests have similar accuracy for detection of advanced fibrosis. Future studies are needed to devise more effective noninvasive fibrosis markers in this population.
4-R Poster: Type 2 Diabetes Mellitus is Associated with Significantly Higher Risk of Mortality and Extra-hepatic Cancers in Biopsy-proven Non-advanced Nonalcoholic Fatty Liver Disease

Presenter: Joud Arnouk, Resident

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Jaideep Behari PhD

Authors: Joud Arnouk MD, Diana Marie Jaiyeola MD, Krupa Patel MD, Vikrant Rachakonda MD, Jaideep Behari PhD

Introduction: Nonalcoholic fatty liver disease (NAFLD) and Type 2 diabetes mellitus (DM) are closely linked but the impact of DM on patients with NAFLD with non-advanced fibrosis is unclear. Our aim was to determine the impact of DM on overall mortality and incidence of major clinical events in patients with biopsy proven, non-advanced NAFLD.

Methods: We identified 556 NAFLD patients seen at the University of Pittsburgh Medical Center between May 2007 and September 2017, with a liver biopsy showing non-advanced fibrosis (defined as Metavir stage F0-F2). We recorded demographic and clinical information and clinical outcomes, including survival, extra-hepatic malignancy and liver-related outcomes (defined as development of cirrhosis, portal hypertension, liver cancer, and liver transplant). DM was defined as an established diagnosis of “Diabetes mellitus” in the electronic health record, Hemoglobin A1c = 6.5, or concurrent anti-diabetic medication use. Categorical variables were compared using Fisher exact tests. Continuous variables were compared with Welch’s T tests or Mann Whitney U tests for non-normally distributed variables. Kaplan Meier methods with Cox Proportional Hazards models were used to analyze overall and event-free survival.

Results: At the time of biopsy, 126 patients (22.7%) had DM while 430 (77.3%) did not. Patients with DM were older [52.8 (50.6-54.9) years vs 48.4 (47.2-49.6) years, p=0.004], and had higher BMI [35.2 (34.0-34.3) kg/m² vs 33.3 (32.7-34.0) kg/m²]. DM patients had more severe steatosis and stage 2 fibrosis, as well as NAS scores [4.9 (4.7-5.2) vs 4.4 (4.3-.45), p=0.001]. Over a mean follow-up period of 5.39 (95% CI 5.10-5.69) years, the overall mortality rate in NAFLD patients with DM was over twofold higher than in those without DM (1.5% vs. 0.6%, p =0.0094). In multivariate analyses, age [HR 1.056 (1.013-1.100), p=0.011], tobacco use [HR 3.572 (95% CI 1.356-9.411), p=0.010] and diabetes [HR 2.493 (1.070-5.808), p=0.034] were independently associated with mortality. For non-hepatic malignancies, NAFLD patients with DM had three-fold higher rates compared to those without DM (1.8% vs 0.6%, p=0.0030). Only age [HR 1.045 (1.005-1.087), p=0.026] and baseline DM [HR 2.249 (1.007-5.027), p=0.048] were independently, positively associated with development of non-hepatic malignancies, while female gender [HR 0.833 (0.192-3.612), p=0.007] was protective. The overall rate of liver-related outcomes was 0.9% and did not differ between NAFLD patients with or without DM.

Conclusion: In patients with biopsy-proven non-advanced NAFLD, DM is associated with significantly greater risk of mortality and extra-hepatic cancers, but not liver-related outcomes, over 5 years. Therefore, concurrent DM identifies a subgroup of non-advanced NAFLD patients at significantly higher risk of worse short-term outcomes.
**Poster Abstracts**

5-R  **Poster:** Dynamic Changes in Peri-Operative Hemodynamic Parameters May be Associated with Predictors of RV Failure Within First Year After LVAD Implantation

**Presenter:** Zubair Bashir, Resident

**Research Interest:** Clinical Cardiology

**Mentors:** Marc Simon MD

**Funding Source:** R01 AG-058659, P01 HL-103455-02

**Authors:** Zubair Bashir MD, Tim Bachman MS, Lauren Williams, C Vu, Y Shwetar, Robert Kormos MD, Marc Simon MD

**Introduction:** Right Ventricular failure (RVF) is a common complication of left ventricular assist device (LVAD). It reflects high burden of mortality and morbidity in the immediate post-surgical period. Various studies have investigated perioperative predictive risk factors and strategies to counter RVF in the immediate post-operative period. In our study, we analyzed peri-operative hemodynamic parameters of patients who experienced RVF beyond the immediate postoperative period to include up to one year after surgical implantation.

**Methods:** Invasive hemodynamic data were obtained for patients at two time points: T(1) retrospectively from right heart catheterization during pre-LVAD evaluation and T(2) prospectively in the perioperative setting with patients under anesthesia, pre-sternotomy. Standard hemodynamic parameters, along with pulmonary artery (PA) pulse pressure, PA pulsatility index (PAPI), and central venous pressure (CVP) to pulmonary capillary wedge pressure (PCWP) ratio were measured at each time point. The change for each parameter between time points was also calculated. Patient outcomes were obtained by reviewing electronic health records. The diagnosis of RVF was made based on the symptoms, need for IV diuretics or inotropes. Mann-Whitney U test was performed to compare RV Failure vs no RV Failure groups at both individual time points and the changes in values between time points.

**Results:** Data were obtained for 52 patients (age 57±12, 9 females). Eight patients (4 females), were determined to be admitted to the hospital with symptoms of RV failure within the 1st year post-implant. Significance was found for changes between pre and intra-operative time points in mean aortic pressure and heart rate (table1).

**Conclusion:** This pilot study suggests that there may be an association between patients’ peri-operative pulmonary arterial hemodynamic changes with LVAD support and re-hospitalizations due to RV failure within the first year following LVAD implantation. Dynamic assessment of hemodynamic response to LVAD may be helpful for risk assessment and patient management. Ongoing work is assessing additional time points during implantation as well as additional parameters of hemodynamic load.
**Poster: Evaluating Contraception Counseling in the Rheumatology Outpatient Setting: A Qualitative Study of Reproductive-Age Women with Rheumatic Diseases**

**Presenter:** Alaina Chodoff, Resident

**Research Interest:** Clinical Rheumatology and Clinical Immunology

**Mentors:** Mehret Birru Talabi MD

**Authors:** Alaina Chodoff MD, Olivia Stransky MPH, Mehret Birru Talabi MD

**Introduction:** Many women with rheumatic diseases are diagnosed during their reproductive years and yet little is known about what patients expect of their rheumatologists regarding family planning counseling and reproductive health care. Peripartum safety issues are of particular concern for women with rheumatic diseases given the delicate balance between adverse maternal/fetal outcomes from undertreated disease and the potential teratogenicity of immunosuppressive therapy. We conducted a qualitative study to assess patient's views on inclusion of rheumatologists in family planning care including contraception, pregnancy planning and reproductive concerns. This preliminary analysis focuses on patients’ experiences with contraceptive care in rheumatology outpatient settings.

**Methods:** This study was approved by the University of Pittsburgh IRB. A diverse sample of female patients ages 20-45 were recruited from 2 UPMC rheumatology clinics in Pittsburgh, PA. Women provided verbal or written consent to participate in thirty-to-forty-five minute, audio-recorded, semi-structured interviews. Interviews were conducted by trained staff member by phone, and transcribed verbatim. A deductive approach was used to create a preliminary codebook to evaluate women’s experiences with contraception care; new codes were added, existing codes were refined, and final codes were categorized into major themes.

**Results:** Our sample was composed of 12 women with various underlying autoimmune diagnoses, among which 2 were currently pregnant, 1 was pregnant after diagnosis, 4 were pregnant before diagnosis and 5 were never pregnant. The average age of women was 33. Eleven out of 12 patients used contraception currently or had ever used contraception and 4 women had at least one unintended pregnancy. Three themes emerged from the interviews; women: 1) felt comfortable discussing their pregnancy intentions with rheumatologists, 2) rarely discussed contraception methods or initiation with their rheumatologists; 3) were unclear about the effects of contraception on treatment. Only one patient had ever discussed contraception with her rheumatologist, who was able to provide “reassurance about questions I had about if taking a hormonal contraceptive would adversely affect my condition.”

**Conclusion:** While most women in this study would inform their rheumatologists if they wished to become pregnant, women very rarely discussed contraception or pregnancy avoidance with rheumatologists. However, women were concerned about the effects of their contraceptive methods on their rheumatic diseases. Rheumatologists may consider broadening their counseling to include contraception safety among reproductive-age women with rheumatic diseases.
**Poster: Does Inflammation in IBD “Burnout” Over Time?**

**Presenter:** Hassieb Din, Resident

**Research Interest:** Clinical General Internal Medicine

**Mentors:** David Binion MD

**Authors:** Hassieb Din MD, Alyce Anderson PhD, Claudia Ramos Rivers MD, Dmitriy Babichenko PhD, Gong Tang PhD, Ioannis Kouroubakis MD, Marc Schwartz MD, Siobhan Proksell MD, Elyse Johnston MD, Arthur Barrie MD, Janet Harrison MD, Jana Hashash MD, Michael Dunn MD, Douglas Hartman MD, David Binion MD

**Introduction:** Given the aging US population, patients with inflammatory bowel disease (IBD) are also growing older and are experiencing increased duration of their illness. There is limited information on the effects of prolonged disease duration on IBD natural history. The aim of this study was to assess changes in disease severity over time by comparing patients with longer and shorter durations of IBD.

**Methods:** A retrospective analysis of markers of inflammation, quality of life, disease activity, medication usage, and healthcare utilization between 2009-2017 was conducted on consented IBD patients followed prospectively in a natural history registry at a tertiary care center. Duration of disease was calculated from documented year of IBD onset, and patients were divided into quartiles (>22 years, 15-22 years, 9-14 years, and <9 years). Only patients with at least 3 years of clinical follow up were included. For analysis, the top quartile (>22 years with IBD) was compared to the bottom quartile (<9 years with IBD).

**Results:** A total of 1411 IBD patients were included (>22 years with IBD, n=712; <9 years with IBD, n=699). Those with longer disease duration were older (p<0.001) with increased frequency of Crohn's disease compared to ulcerative colitis (p<0.001). Shorter disease duration had higher medication utilization (biologics, p=0.007; immunomodulators, p<0.001; systemic steroids, p=0.003; 5-aminosalicylic acid agents, p<0.001). Patients with shorter disease duration also experienced more frequent elevations of ESR (p<0.001), CRP (p<0.001), and monocytosis (p=0.001). Paradoxically, patients with longer duration of Crohn's disease had higher disease activity scores (i.e. mean Harvey Bradshaw scores), which include measures of daily diarrheal bowel movements, abdominal pain, and well-being (p<0.001). Those with a longer course of IBD demonstrated increased anti-depressant (p=0.02), narcotic (p<0.001), and antibiotic (p=0.02) usage. There was no difference in quality of life (mean SIBDQ) between shorter and longer duration IBD. While there was no significant difference in healthcare charges, patients with shorter duration of IBD did visit the emergency room more frequently (p=0.005).

**Conclusion:** These data suggest that IBD patients may experience less severe inflammation and “burnout” over time. Furthermore, the increased use of anti-depressants, narcotics, and antibiotics in those with longer disease duration may point towards the sequela of long-term inflammation and cumulative damage within the gut, negatively impacting those with longer duration of Crohn's disease. While our results could be due to patients with longstanding IBD achieving more stable remission and experiencing less flare over the study period, further research describing the consequences of increased disease duration are needed to help guide future therapeutic strategies.
**Poster: Natural History of Diabetes Mellitus and Inflammatory Bowel Disease: Increased Disease Severity, Worse Quality of Life, and Under-Treatment with Immunomodulator and/or Biologic Agents**

**Presenter:** Hassieb Din, Resident  

**Research Interest:** Clinical  
**General Internal Medicine**

**Mentors:** David Binion MD

**Authors:** Hassieb Din MD, Alyce Anderson PhD, Claudia Ramos Rivers MD, Siobhan Proksell MD, Tariq Salim MD, Dmitriy Babichenko PhD, Gong Tang PhD, Ioannis Koutroubakis MD, Marc Schwartz MD, Elyse Johnston MD, Arthur Barrie MD, Janet Harrison MD, Michael Dunn MD, Douglas Hartman MD, David Binion MD

**Introduction:** The prevalence of diabetes mellitus (DM) is rising and is known to increase systemic inflammation in chronic inflammatory disorders, such as rheumatoid arthritis and psoriasis. There is limited data regarding the effect of DM on inflammatory bowel disease (IBD) severity. We sought to characterize multi-year patterns of inflammation, quality of life, medication use, and healthcare utilization between IBD patients with and without DM.

**Methods:** Consented IBD patients followed prospectively in a natural history registry at a tertiary center between 2009-2017 were analyzed. Patients with ≥3 years of clinical follow up were included. A diagnosis of DM was determined through ICD9/10 codes, laboratory markers based on American Diabetes Association criteria, and use of anti-hyperglycemic agents. The study cohort was compared to 400 randomly selected IBD controls without a diagnosis of DM, no laboratory evidence of hyperglycemia, or history of anti-hyperglycemic treatment. Subgroup analysis was performed among diabetics with poor glycemic control (hemoglobin A1c >7) vs. adequate glycemic control.

**Results:** Out of 2810 IBD patients, 5% (n=141) had DM (IBD DM; 44% Ulcerative Colitis, 56% Crohn’s disease, 48.2% female). Compared with IBD controls, IBD DM patients were older (p<0.001) with a higher mean body mass index (p<0.001). IBD DM had higher use of 5-aminosalicylic acid (5ASA) agents (p=0.04), narcotics (p<0.001), and antibiotics (p=0.007) but not immunodulators and/or biologics. When analyzing biomarkers of severity, IBD DM demonstrated higher frequencies of elevated CRP (p=0.006), elevated ESR (p=0.001), eosinophilia (p=0.004), monocytosis (p=0.02), and hypoalbuminemia (p=0.001). IBD DM had worse quality of life (mean SIBDQ; p<0.001). IBD DM had increased healthcare utilization compared with controls (emergency room usage (p=0.008), hospitalizations (p<0.001), gastroenterology clinic visits (p<0.001), and median annual charges (p<0.001)). Among diabetics, poor glycemic control was not associated with any of these clinical severity parameters. Furthermore, among IBD DM patients, use of biologics and/or immunomodulators was not associated with a further increase in antibiotic use or hospitalizations.

**Conclusion:** DM in IBD is associated with increased disease severity. Furthermore, diabetics were more frequently treated with 5ASA agents, but not immunomodulators and/or biologics, even though their IBD activity appeared to be significantly worse. Use of immunomodulators and/or biologics did not demonstrate an increased safety signal in the IBD DM patients using these agents. Overall, DM appears to be linked to a worsened IBD course and further studies are warranted to investigate if more effective IBD treatment strategies can be safely implemented to improve outcomes in this group.
**Poster: Risk Stratification of Hürthle Cell Neoplasms Using Thyroseqv3**

**Presenter:** Reed Doerfler, Resident

**Research Interest:** Clinical Endocrinology and Metabolism

**Mentors:** Pooja Manroa MD

**Authors:** Reed Doerfler MD, Linwah Yip MD, Marina Nikiforova MD, Yuri Nikiforov MD, Pooja Manroa MD

**Introduction:** Hürthle cell carcinomas (HCC) are known to be more aggressive and have a higher rate of distant metastasis compared to other differentiated thyroid cancers. They are diagnosed usually after histologic evaluation of a thyroid nodule that is classified as a Hürthle cell (oncocytic) neoplasm (HCN) on fine needle aspiration (FNA) biopsy. Thyroseqv3 (TSv3) is a next-generation sequencing based molecular test which can detect thyroid cancer-related mutations as well as copy number alterations (CNA) with characteristic patterns that are associated with HCC. The aim of the study is to evaluate the accuracy of TSv3 in predicting benign versus malignant HCN.

**Methods:** We retrospectively identified 19 patients who had histologic HCC and 7 patients with Hürthle cell adenoma (HCA) who had thyroidectomy from August 2008-August 2018 TSv3 testing of thyroid nodule FNA biopsies preoperatively. Sensitivity and specificity for TSv3 to predict malignancy were calculated. The association between presence or absence of CNA and risk of recurrence based on the American Thyroid Association (ATA) classification was also assessed.

**Results:** The nodule size was similar in both groups (mean for HCC 3.69 cm vs. 3.35 cm for HCA, p =0.76). HCC was more common in men (53% vs 47% female) with similar age of patients in both groups (mean age at time of surgery for HCC 53.7 vs. 58.9 years for HCA, p=0.43). Positive TSv3 results were obtained in 17 (89%) HCC and 2 (29%) HCA nodules (p =0.0057). Thus, TSv3 for malignancy in HCN was associated with a sensitivity of 89%, specificity of 71% and accuracy of 92%. Of the 2 HCC with TSv3 negative results, one had low level CNA and one had an isolated EIF1AX splice mutation. Both were considered "currently negative" although ongoing surveillance was recommended due to the presence of a clonal genetic alteration. Of the 7 HCA nodules with TSv3 results, 4 had no mutations, 2 had EIF1AX splice mutations, and one had an EZH2 mutation. Interestingly, CNA were more frequently detected in HCC (15/19, 79%) vs. 2/7 (29%) (p =0.028). There was no significant relationship between positive CNA status and higher risk of recurrence by ATA classification (p =0.53).

**Conclusion:** In a consecutive series of patients with HCN and TSv3, molecular testing predicted malignancy with both high sensitivity (89%) and specificity (71%). Diagnostic thyroid lobectomy has been the standard of care so far for HCNs, and better risk stratification with molecular testing may provide personalized patient management options.
**Poster Abstracts**

12-R **Poster:** Patterns and Location of Post-Operative Recurrence in Crohn’s Disease Patients with Side to Side Anastomosis Following Ileocecal Resection

**Presenter:** Furkan Ertem, Resident

**Research Interest:** Clinical General Internal Medicine

**Mentors:** David Binion MD

**Funding Source:** Private Source

**Authors:** Furkan Ertem MD

**Introduction:** The majority of Crohn’s disease (CD) patients with ileocecal disease will develop strictures requiring surgery and anastomosis. Side-to-side anastomosis (STSA) reconstructs longitudinal segments of bowel next to one another in an anti-peristaltic orientation using a linear stapler. Longer staple lines were previously advocated to create wide lumen anastomoses with the goal of preventing CD recurrence. Patterns and specific location of CD recurrence in the STSA have not been fully defined (i.e. is CD recurrence along the anastomotic staple line vs. the neo-terminal ileal (neo-TI) inlet). We sought to identify patterns of CD recurrence and the specific site of recurrence (i.e. neo-TI inlet vs staple line) among patients with STSA.

**Methods:** We conducted an observational study of consented CD patients who underwent ileocecal resection and STSA and were followed post-operatively between 2009-2016. Surgical technique, post-operative therapy and endoscopic evaluation was at the discretion of treating physicians. Demographics, clinical characteristics, health care utilization and disease activity of patients were collected. Site of recurrence was determined by colonoscopic assessment. Postoperative CD recurrence was defined as a Rutgeerts score =2. Patients with ≥2 years of follow-up data were included.

**Results:** 82 CD patients undergoing ileocecal resection with STSA formed the study group. Mean follow up time for this cohort was four years (53.1 months ± 23.9 vs 44.5 ± 26.2). During longterm followup, 65% of the STSA patients experienced postoperative CD recurrence (n=54) while 35 % (n=28) remained in remission. Among these patients with and without recurrence, there was no difference in current age in years (44.8 ± 12.4 vs 43.8 ± 13.1), age at diagnosis (22.6 ± 10.2 vs 20.7 ± 9.8), BMI (24.7 ± 5.2 vs 24.8 ± 8.0), time to surgery in years after diagnosis (11.8 ± 10.0 vs 12.2 ± 10.4), smoking status (40 % vs 22%), time to first corticosteroid (CS) after surgery in months (26.6 ± 20.8 vs 21.4 ± 20.7), and duration of postoperative follow up in months (53.1 ± 23.9 vs 44.5 ± 26.2). STSA patients with CD recurrence had higher postoperative exposure to Anti-TNF (88 % vs 57%, p=0.055) but this did not reach statistical significance. Lastly, the anastomotic inlet of the neo-TI was the most common site for the CD recurrence and not the anastomotic staple line (81% vs 19%, respectively).

**Conclusion:** This multiyear observational cohort study demonstrates that the majority of patients with STSA had postoperative CD recurrence. 80% of STSA CD recurrence occurs at the neo-TI inlet, and not the anastomotic staple line. Treatment decisions guided by post-op colonoscopic surveillance must assess the neo-TI inlet in CD patients with STSA.
**Poster: Frontline Health Workers’ Perceptions of Asynchronous Teleconsultations**

**Presenter:** Steven Fox, Resident

**Research Interest:** Clinical
General Internal Medicine

**Mentors:** Timothy Girard MD

**Authors:** Steven Fox MD, Erin Kim BA, MPH, Meghan Moretti MS, FNP-BC, Michelle Turner BS, MSHS, Timothy Girard MD, SCI, Stephen Y Chan MD, PhD

**Introduction:** There is a shortage of physicians (primary care and specialist) worldwide, particularly in rural areas and in low- and middle-income countries. Telemedicine may improve access to medical care in those regions. Asynchronous teleconsultation, also known as store-and-forward telemedicine, is a model of telemedicine that involves partnerships between a frontline health worker or hospital/clinic with a network of expert consultants who provide consultation on challenging cases. The Addis Clinic forms partnerships for asynchronous teleconsultation between several hospitals/clinics in low- and middle-income countries and a network of expert consultants. We sought to assess frontline health workers’ perceptions of asynchronous telemedicine.

**Methods:** We reviewed surveys of frontline health workers that were distributed 21 days after a teleconsultation. We analyzed data regarding frontline health workers’ perceptions on whether or not the consultation was completed sufficiently quickly, clarified the diagnosis, assisted in management, helped improve the patient’s symptoms or function, reduced costs for the patient or hospital/clinic, and/or provided educational benefit. We also sought to determine where these outcomes varied among different partner sites. The percentage of “yes” responses to each question was determined for each partner, and the standard deviation of these values was calculated to quantify the degree of variation among partner sites.

**Results:** Out of 558 total cases completed between April 25, 2017 and November 25, 2018, 61 follow-up surveys were completed by frontline health workers at 10 different partner sites (11% survey response rate). Respondents indicated that the consultation was provided sufficiently quickly in 100% of cases (s = 0.0). They believed the consultation clarified the diagnosis in 90.2% (s = 31.4%), aided in management in 90.2% (s = 14.6%) improved the patient’s symptoms in 72.1% (s = 24.2%) resulted in a cost saving to the local hospital or clinic in 55.7% (s = 46.6), and provided educational benefit in 98.4% (s = 4.5%).

**Conclusion:** We found that a high percentage of frontline health workers believed that asynchronous teleconsultation clarified diagnoses, assisted in management, improved symptoms, and had educational benefit. The most consistent results were noted for educational benefit. In some cases, respondents perceived cost savings, but this varied among partner sites. Further research is needed to identify partner and patient characteristics associated with better outcomes, and to identify potential quality improvement interventions.
**Poster Abstracts**

**14-R Poster:** Can We Develop Precision Medicine for Biologic Selection in IBD Based on Routinely Available Clinical Information? Using Big Data Analytics to Identify Predictors of Anti-TNF Response.

**Presenter:** Scott Friedberg, Resident

**Research Interest:** Clinical General Internal Medicine

**Mentors:** David Binion MD

**Funding Source:** W81XWH-11-2-0133, W81XWH-17-1-0556

**Authors:** Scott Friedberg MD, Claudia Ramos-Rivers MD, Weston Bettner MD, Marc Schwartz MD, Dmitriy Babichenko PhD, Gong Tang PhD, Michael Dunn MD, Ioannis Koutroubakis MD, David Zepeta MD, Michelle Luo PhD, David Binion MD

**Introduction:** Precision medicine rationally guides therapeutic selection based on objective markers to optimize treatment success. The need for precision medicine in IBD has increased with the advent of biologic agents with different mechanisms of action, which may only be relevant in subgroups. Barriers to developing precision medicine in IBD include the lack of a scale to gauge treatment response, lack of multi-year natural history datasets and lack of candidate markers to identify subgroups. We analyzed IBD patients initiating anti-TNF therapy to determine which routinely available clinical metadata would function as a barometer of treatment response and explored initial biomarkers to identify subgroups with higher or lower chances of response.

**Methods:** This was an observational study from a consented, prospective, IBD natural history registry. Electronic medical record data was curated and transformed into metadata (i.e. patterns of clinical data) as described previously. Patients naïve to anti-TNF therapy were identified and metadata from the year prior to anti-TNF therapy was compared with the year after anti-TNF initiation. Treatment response was assessed with quality of life, disease activity scores, anemia, biochemical markers of inflammation, steroid requirement, narcotic use, and total healthcare charges. The McNemar test was used to compare the two years.

**Results:** 841 IBD patients naïve to anti-TNF therapy were analyzed (640 CD, 201 UC; Mean age 35 ± 12y (S.D.); 52% female). When the total group was analyzed, anemia, high CRP, high ESR 33%, mean SIBDQ and disease activity UCAI>3 /HBI>4 demonstrated improvement but not healthcare charges before and after anti-TNF initiation. Prior to anti-TNF start, 12.2% (n=103) patients had peripheral eosinophilia and 19.8% (n=167) had monocytosis. Within eosinophilia IBD, there was no significant improvement in clinical parameters before and after the initiation of anti TNF. In contrast, for monocytosis IBD, there was significant improvement in the majority of clinical parameters, including high CRP, high ESR, mean SIBDQ, anemia, average total healthcare charges.

**Conclusion:** Metadata derived from inflammatory markers, anemia, quality of life, disease activity and total healthcare charges functions as a barometer of biologic treatment response in IBD. Furthermore, the presence of eosinophilia predicts diminished response while monocytosis is associated with increased response to anti-TNF therapy in IBD.
Poster: Peripheral Blood Eosinophilia Functions as a Candidate Biomarker of Decreased Response to Anti-TNF Therapy in Crohn's Disease

Presenter: Scott Friedberg, Resident

Research Interest: Clinical General Internal Medicine

Mentors: David Binion MD

Funding Source: W81XWH-11-2-0133, W81XWH-17-1-0556

Authors: Scott Friedberg MD, Weston Bettner MD, Claudia Ramos-Rivers MD, Ioannis Koutroubakis MD, Gong Tang PhD, Dmitriy Babichenko PhD, Siobhan Proksell MD, Elyse Johnston MD, Marc Schwartz MD, Jana Hashash MD, Arthur Barrie MD, Janet Harrison MD, Doug Hartman MD, Michael Dunn MD, David Binion MD

Introduction: There is an urgent need for biomarkers which can rationally guide treatment selection of mechanism-based therapeutics in Crohn's disease (CD). There is new appreciation of peripheral blood eosinophilia (PBE) as a biomarker of severity in chronic inflammatory diseases, including asthma. Emerging data suggests that PBE in CD identifies a patient subgroup with aggressive disease, at risk for increased healthcare utilization. We sought to determine whether CD patients with or without PBE would be associated with a differential response to initial anti-TNF therapy in a real-world setting.

Methods: This was an observational study from a consented, prospective, IBD natural history registry. CD patients naïve to anti-TNF therapy were identified and metadata from the year prior to anti-TNF therapy was compared with the year after anti-TNF initiation. Treatment response was assessed with disease activity scores (HBI), quality of life scores (SIBDQ), biochemical markers of inflammation (CRP, ESR, hemoglobin and albumin), steroid requirement and patterns of healthcare utilization. Outcomes were measured as no improvement, partial improvement and full improvement/normalization between the two years.

Results: There were data on 668 CD patients available for analysis (Female 51.8%, median age 37 (IQR 27 – 47), median duration of disease 10 years (IQR 5, 7.5years); age of diagnosis 23 (IQR 17-32)). PBE was identified in 155 CD patients (23.2%) who received anti-TNF therapy. Initiation of anti-TNF was associated with clinical benefit in the majority of CD patients in the total cohort, with improvement in mean SIBDQ (62%), mean HBI (70%) and reduction of steroid use (31%). There was evidence of loss of response, leading to switching of anti-TNF in 17% or discontinuation of anti-TNF in 17%. We next examined whether there was a differential response between CD patients with and without PBE. There was no difference regarding disease activity scores (mean HBI), quality of life scores (mean SIBDQ), steroid use, or lab parameters (albumin, hemoglobin). PBE CD patients had increased need to switch anti-TNF agents (p<0.02), increased ER utilization (p<0.0005) and increased need for hospitalization (p<0.0001).

Conclusion: PBE is present in approximately one-quarter of CD patients. CD patients with PBE demonstrate a decreased response to initial anti-TNF therapy, which is associated with a higher rate of healthcare utilization compared with CD patients without PBE in the year following initiation of treatment. Future prospective studies in the PBE CD patient population are needed to fully define the role of this biomarker as predictor of anti-TNF treatment.
**Poster Abstracts**

16-R  **Poster:** Empiric Antimicrobial Therapy and Clinical Outcomes of Infections Due to ESBL-Producing Klebsiella Pneumoniae

**Presenter:** Ayako Wendy Fujita, Resident

**Research Interest:** Clinical Infectious Diseases

**Mentors:** Yohei Doi MD

**Authors:** Ayako Wendy Fujita MD, Lloyd G Clarke B.Sc., Yohei Doi MD

**Introduction:** Extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E) are a global health problem, colonizing approximately 1 billion people. When invasive infection develops from these organisms, carbapenems are the treatment of choice. However, clinical data supporting this practice are generated largely from cases caused by Escherichia coli. In high inoculum infections such as pneumonia, where the predominant ESBL-E is Klebsiella pneumoniae, few data exist regarding the efficacy of non-carbapenem beta-lactams for empiric treatment. In this study, we described demographic data, empiric treatments, and clinical outcomes of patients infected with ESBL-producing K. pneumoniae infections at University of Pittsburgh Medical Center (UPMC)-Presbyterian Hospital.

**Methods:** This is a retrospective, descriptive study at UPMC-Presbyterian in Pittsburgh, PA. Adult patients diagnosed with ESBL-producing K. pneumoniae infections were included based on existing medical records. Microbiological data was extracted from the laboratory reporting system, “Sunquest,” based on the organism (K. pneumoniae), and ESBL positivity tested in accordance with the CLSI recommendations. Only inpatient admissions were included, and carbapenem-resistant cases were excluded. Types of cultures included blood, respiratory (sputum, tracheal aspirate, BAL), urine, and wound (superficial, deep). Only one type of culture per patient was included; if more than one type resulted for a patient, only the first was included. Demographic and clinical data were collected from MARS, entered into RedCap, and analyzed using Microsoft Excel. The study was approved by the University of Pittsburgh IRB.

**Results:** Records from September 2016-August 2018 were reviewed. Fifty-five patients had an ESBL-producing K. pneumoniae infection. Patients were excluded who were considered colonized by the organism and therefore not treated; treated with inappropriate definitive therapies; or were discharged before final susceptibilities. Twenty-two patients met inclusion criteria. Five infections were from blood, 9 from respiratory cultures, 4 from urine, 3 from wounds. Of the bacteremia cases, sources included pneumonia, intraabdominal, and intravenous catheters. Median age of patients was 67.5 years. Average Charleston Comorbidity Index was 5. Empiric treatment was divided between three classes: BL-BLI (n=10, 45.5%), cephalosporins (n=6, 27.3%), and carbapenems (n=6, 27.3%). Six patients (27.3%) died during hospitalization. Average hospital length-of-stay was 40 days.

**Conclusion:** Although infections with ESBL-producing K. pneumoniae are uncommon, patients with these infections have high mortality and prolonged hospitalizations. Treatment practices, including which infections are considered colonization versus true infection, as well as choice of empirical therapy, vary widely at our institution. Data are still needed to assess mortality outcomes in patients treated empirically with carbapenems versus non-carbapenems, particularly in high-inoculum infection sites such as pneumonia.
**Poster:*** Multi-Organ Failure is the Strongest Determinant of Poor Clinical Outcomes in Acute Pancreatitis (Apprentice Study Group)

**Presenter:** Amir Gougol, Resident

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

**Mentors:** Georgios Papachristou MD

**Funding Source:** VA Merit

**Authors:** Amir Gougol MD, Pedram Paragomi MD, Gong Tang PhD, Anna Evans Phillips MD, Ioannis Pothoulakis MD, Xiaotian Gao MS, Rupiyoti Talukdar MD, Rakesh Kochar MD, Mahesh Kumar Goenka MD, Aiste Gulla MD, Jose A. Gonzalez MD, Vikesh K. Singh MD, Miguel Ferreira MD, Tyler Stevens MD, Georgios Papachristou MD

**Introduction:** According to the revised Atlanta classification, severe acute pancreatitis (AP) is defined by the development of persistent organ failure (OF); however, there is remarkable heterogeneity within this group of patients. In this study, we aim to assess the impact of multi-organ failure (MOF) with its various presentations on clinical outcomes in patients with severe AP.

**Methods:** Data was collected from a multinational, prospective cohort of AP patients (APPRENTICE Study). Enrollment was conducted between May 2015 to November 2017. There were 22 international centers who participated from 4 different continents. Renal, pulmonary, and cardiovascular failure were defined by the modified Marshall Score =2. Isolated organ failure (IOF) involved a single failing organ; multi-organ failure (MOF) was defined by the failure of =2 organs. Patients with MOF were categorized based on the type of organ, which failed first. Early OF was defined as the development of OF within the first 24 hours of admission.

**Results:** In total, 1585 patients were enrolled; median age was 49.8, 47% were female and biliary was the most common etiology (45.3%). Overall, 39 (2.5%) patients died during hospitalization. Persistent OF developed in 188 (11.8%) patients. Of them, 89 (47.3%) patients developed MOF, whereas 99 (52.6%) patients were classified as IOF. Mortality was significantly higher in patients with MOF compared to IOF (37.5% vs. 7.1%, p-value<0.01). Of patients with IOF, the renal system was involved in 20.2%, pulmonary in 74.7%, and cardiovascular in 5% of patients. Overall, the mortality among patients with IOF was relatively low (7.1%) and similar between isolated renal and pulmonary failure (5% vs. 4.1%, p-value=0.8). Among patients with MOF, the first failing organ was renal in 24 (27%), pulmonary in 25 (28%), and cardiovascular in 4 (4.5%) patients. In 36 (40.5%) subjects, OF started in multiple organs concurrently (concurrent OF). OF onset varied based on the type of first failing organ. Development of early OF occurred less frequently in patients with pulmonary as the first failing (37.5%), compared to patients with renal (71%) or concurrent (73%) as the initial failing organ (p-value=0.01). After controlling for the number of failing organs, mortality was significantly higher in patients with pulmonary as the first failing organ compared to patients with renal as the first failing organ (62.5%, vs. 25%, p-value=0.01).

**Conclusion:** Using a large, international, prospective cohort of AP patients, we demonstrated heterogeneous outcomes in patients with severe AP; MOF had the highest impact on mortality. The clinical course of patients with MOF appeared to varied based on the type of first failing organ.
Introduction: Colonoscopy is the gold standard for assessing clinical status in inflammatory bowel disease (IBD), allowing gastroenterologists to gauge level of disease activity and assess for the presence of enteric infection. Clostridium difficile (C diff) is the most important enteric pathogen in IBD, occurring frequently and worsening its disease course. The classic endoscopic feature of C diff infection is the pseudomembrane, found in up to 60% of infections in the general population but only 13% of the IBD population. There is limited data characterizing other endoscopic lesions/features which may be more commonly associated with C diff in IBD. Aim: Define colonoscopic features of C diff infection in IBD patients and IBD controls matched for severity using propensity score matching.

Methods: Data from a consented, IBD natural history registry was used to identify patients with a confirmed molecular laboratory diagnosis of C diff infection. The comparable control cohort was generated using nearest neighbor propensity score matching for all known risk criteria for C diff infection, including age, gender, disease type, years of disease, medication exposure, antibiotic exposure, biomarkers of inflammation, nutritional parameters and healthcare utilization. Out of 67 C diff infected patients, there were 27 who had colonoscopy at the time of or within 1 week of diagnosis. Two disease severity matched controls undergoing colonoscopy were analyzed for each C diff case. Endoscopic documentation from PROVATION software was analyzed for the presence or absence of specific IBD features including pseudomembranes, mucopus, adherent mucus, aphthous ulcers, shallow ulcers, deep ulcers, friability and erosions.

Results: Colonoscopic features which differentiated IBD C diff infection from IBD controls included the presence of adherent mucus (22.2% cases compared to 5.6% controls; p = 0.0188) and shallow ulcers (40.7% cases compared to 11.1% controls; p = 0.004). The overall rate of pseudomembrane detection in the IBD C diff patients was 7.4%, which was identical to the IBD controls. When pseudomembranes, mucopus and adherent mucus were grouped together as an exudative lesion, this was seen in double the number of C diff IBD cases (33%) compared with IBD controls (16%; p=0.061). Other endoscopic markers of IBD activity, including friability, deep ulcers, aphthous ulcers and erosions were equally distributed between the IBD patients with and without C diff.

Conclusion: The colonoscopic features significantly associated with CDI in patients with IBD are adherent mucus and shallow ulcers. Pseudomembranes are not the most common exudative lesion in IBD C diff infections. The lack of definitive C diff endoscopic features reinforces the need for confirmatory stool testing in the IBD patient population.
**Poster Abstracts**

**24-R Poster:** The Evolution of Radiographic Edema in ARDS and Its Association with Clinical Outcomes: A Prospective Cohort Study in Adult Patients

**Presenter:** Daniel Kotok, Resident

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Georgios D. Kitsios MD, PhD

**Authors:** Daniel Kotok MD, John Evankovich MD, William Bain MD, Daniel G. Dunlap MD, Faraaz Shah MD, MPH, Sarah F. Rapport BS, MPH, Libing Yang MDc, Yingze Zhang PhD, Janet S. Lee MD, Alison Morris MD, MS, Bryan J. McVerry MD, Georgios D. Kitsios MD, PhD

**Introduction:** Quantification of radiographic edema is not routinely used for risk stratification in Acute Respiratory Distress Syndrome (ARDS). The semiquantitative Radiographic Assessment of Lung Edema (RALE) score has been correlated with degree of hypoxemia and adverse clinical outcomes in a clinical trial population with ARDS. We sought to evaluate the longitudinal evolution of pulmonary edema using the RALE score in a cohort of patients with ARDS, correlating imaging with host-response biomarkers, established ARDS subphenotypes, and clinical outcomes.

**Methods:** We enrolled mechanically-ventilated patients from the University of Pittsburgh Acute Lung Injury Registry and Biospecimen Repository diagnosed with ARDS versus cardiogenic pulmonary edema (controls). RALE scores were assigned for chest x-rays (CXRs) obtained on day of intubation (day 0) and then days 3, 5, 7 and 10 thereafter. CXRs were scored independently by two reviewers. Ten plasma biomarkers of tissue injury and inflammation were measured with a Luminex assay at baseline. We applied a published logistic regression model to classify subjects into hyper-inflammatory vs. hypo-inflammatory subphenotypes (based on concentrations of three variables: interleukin-8 (IL-8), soluble tumor necrosis factor receptor-1 (sTNFR1) and bicarbonate), and demographic, physiologic, clinical outcome data were recorded.

**Results:** RALE scores were calculated for 492 CXRs from 127 patients (105 ARDS and 22 controls, mean age 53, 56% male) with good inter-rater agreement (Pearson r=0.82, p<0.0001). Baseline RALE scores for ARDS patients (23.0±7.7) were significantly higher compared to controls (15.9±5.0, p<0.01). Daily scores displayed a high degree of variability (p<0.001). Among ARDS patients, median RALE scores did not differ by degree of hypoxemia, delivered tidal volume or driving pressure. When adjusted for multiple comparisons, no significant associations with plasma biomarkers or classification to ARDS subphenotypes were detected. Similarly, there were no overall differences in ventilator-free days or 30-day mortality. Interestingly, patients with lower RALE scores had higher sequential organ failure assessment scores (p<0.0001), were more likely to have an indirect mechanism of injury (p<0.01), and a trend toward decreased survival was observed. Early resolution of radiographic edema (defined as ≥25% decrease of baseline RALE score by day 3) was not associated with favorable clinical outcomes.

**Conclusion:** Although the RALE score is easily implementable and with high inter-rater agreement, the lack of associations of RALE scores with ARDS severity groups or prognostic subphenotypes suggest that important interindividual heterogeneity among patients with ARDS may not be captured by radiographic edema alone.
Poster Abstracts

25-R  Poster: Cardiac Resynchronization Therapy Using Pacemakers Versus Defibrillators in Patients with Non-Ischemic Cardiomyopathy: The United States Experience from 2007 to 2014

Presenter: Terence McLaughlin, Resident

Research Interest: Clinical General Internal Medicine

Mentors: Samir Saba MD

Authors: Terence McLaughlin MD, Wendy He MS, Inmaculada Hernandez PharmD, Samir Saba MD

Introduction: Cardiac resynchronization therapy (CRT) and implantable defibrillator therapy often have overlapping indications patients with left ventricular dysfunction. In those with non-ischemic cardiomyopathy (NICM) and dual indications, a CRT-defibrillator (CRT-D) is often recommended over a CRT-pacemaker (CRT-P). However, this recommendation is controversial as data comparing the devices are limited. Hypothesis: There is no difference in all-cause mortality in NICM patients that receive CRT-D rather than CRT-P.

Methods: Using a 5% random sample of Medicare beneficiaries for the years 2007 to 2014, we selected patients with NICM who received a CRT device (1,236 CRT-P and 4,359 CRT-D), excluding those with prior history of ventricular arrhythmias or cardiac arrest. We followed patients from date of CRT device implantation until death or the end of the study period (December 31, 2014). Propensity score matching was performed to control for unbalanced covariates. We examined the difference in all-cause mortality of NICM patients who CRT-P versus CRT-D. Secondary outcomes included time to first inpatient admission, time to first cardiac inpatient admission, total medical costs, total cardiac-related medical costs, and inpatient cardiac-related costs.

Results: At 5 years, 2007 (36%) patients died and 3809 (68%) were hospitalized for any reason while 2504 (45%) were hospitalized for cardiac reasons. Significant baseline differences were noted between the two cohorts. After propensity score matching, CRT-P recipients had similar mortality (HR=1.02 95% CI 0.80—1.31), rates of hospitalization (HR=1.10 95% CI 0.98—1.24) and rates of cardiac hospitalization (HR=1.02 95% CI 0.88—1.17) compared to CRT-D recipients, but a significantly lower cost (delta~ $20,000) of all care and cardiac care at 12 and 24 months after device implantation.

Conclusion: Our results demonstrate that although more expensive, defibrillator therapy is not associated with prolonged survival or decreased risk of hospitalization in CRT recipients with NICM. These results suggest that in patients with NICM and no prior history of ventricular arrhythmias or cardiac arrest, CRT-P devices should be considered. These results have important clinical and economic implications.
**Poster Abstracts**

**26-R Poster:** Long-Term Survival Following Sudden Cardiac Death in Men versus Women: A Single Center Experience from 2002 to 2012

**Presenter:** Terence McLaughlin, Resident

**Research Interest:** Clinical  
General Internal Medicine

**Mentors:** Samir Saba MD

**Authors:** Terence McLaughlin MD, Samir Saba MD

**Introduction:** Sudden cardiac death is a major cause of mortality with estimates of 450,000 deaths annually in the United States. The incidence of sudden cardiac arrest (SCA) differs between the sexes, however, data regarding survival of women compared to men after SCA are conflicting. We therefore examined the long-term survival of women versus men after SCA.

**Methods:** A total of 1,433 (41% women; 44% out-of-hospital SCA) survivors of SCA at our institution between 2002 and 2012 were followed to the primary endpoint of all-cause mortality. Gender differences in survival were examined using Cox regression multivariate models.

**Results:** Women in our cohort were older (p=0.02), less likely to be white (p=0.01), or to have suffered an acute myocardial infarction at the time of SCA (p<0.001). They also had significantly shorter PR (p<0.001) and QRS (p<0.001) durations on their surface electrocardiogram and were more likely to present with an initial ventricular rhythm other than ventricular tachycardia or fibrillation (29% vs. 22%, p=0.001). Consequently, they were also less likely to receive an implantable cardioverter defibrillator (ICD) after the index SCA (22% vs. 31%, p<0.001). Over a median follow-up of 3.6 years, women had worse overall mortality than men (p<0.001). After adjusting for unbalanced baseline covariates, the gender difference in survival disappeared (HR=1.05; 95% CI= 0.85-1.29, p=0.66).

**Conclusion:** Our results demonstrate that although unadjusted data suggest that women have worse survival than men after SCA, this is mainly due to older age, different risk profiles at the time of index event, and differential treatment with ICD. These baseline differences deserve further investigation.
**Introduction:** Continuous glucose monitoring (CGM) is now considered as a standard of care for glycemic status assessment and therapy adjustment in all patients with T1DM and T2DM patients treated with intensive insulin therapy. CGM has been available to people with diabetes for more than a decade, however, it is used by only about 15% in T1DM and fewer in T2DM. There is even more disparity in the access of its availability in the community with low socio-economic status (SES). The purpose of this study was to examine potential benefits of CGM in patients with limited access to technology.

**Methods:** CGM (Freestyle Libre Pro) was placed for 10-14 days in 36 patients, age (mean age 63.4 years +/- 15.4), 61.1% female, BMI (mean 34.2 +/- 8.33 kg/m2 with T2DM (83.4% on Insulin therapy). The patients were asked to keep food and activity logs during the testing period. CGM data was downloaded after the testing period and glucose results were retrospectively reviewed with patients. Individuals also received self-management education. Shared decision making was encouraged to improve knowledge of how their choices affected their diabetes control using CGM data.

**Results:** Thirty Three (91.7%) patients were able to keep the sensor for at least 72 hours and had a follow-up visit with the endocrinologist for interpretation of the data and to discuss therapeutic adjustment of medications and what behaviors may have lead to certain blood glucose patterns based on patient food and activities log and CGM patterns. The Mean A1C at baseline (8.23 +/- 1.88%) slightly improved to mean A1C (7.86 +/- 1.41%) at follow up. (p value 0.28).

**Conclusion:** CGM may be a useful supplement to assess glycemic control, to make therapeutic adjustment and to provide educational feedback on patients’ behaviors among T2DM with low SES who have limited access to technology otherwise. Our study favors a slight improvement in overall glycemic control through patient education and recognition of glucose patterns informed by the professional CGM especially in those with low SES.
**Poster: One Last Breath – Rapid Progression of Idiopathic Pulmonary Fibrosis in a Previously Asymptomatic Patient**

**Presenter:** Neha Mehrotra, Resident

**Research Interest:** Clinical MD  
Pulmonary, Allergy and Critical Care Medicine

**Authors:** Neha Mehrotra MD, Daniel Kotok

**Introduction:** Idiopathic pulmonary fibrosis (IPF) is a progressive, life-threatening, interstitial lung disease of unknown etiology. Although IPF has an overall poor prognosis, the clinical course of individual patients varies from slow progression to acute decompensation, rapid respiratory deterioration and death. We present a case of a patient with IPF that has been clinically stable for a decade after diagnosis. She experienced an acute exacerbation of IPF (AE-IPF) a month after knee surgery, resulting in death within two weeks after admission.

**Methods:** Our patient is a 77-year-old female with history of biopsy proven IPF with no documented flare-ups and stable pulmonary function tests (PFT) for 10 years. She was not on any IPF-related medications and did not require supplemental oxygen. She presented to the emergency department with shortness of breath of acute onset a month after undergoing total right knee arthroplasty. On presentation she was hypoxic, requiring 12 liters of supplemental oxygen to maintain a saturation of 90% on pulse oximetry. Computed tomography angiography did not reveal pulmonary embolism but did show new diffuse ground glass opacities on top of bronchiectasis and honeycombing that was previously documented. Transthoracic echocardiography (TTE) showed left ventricular hypertrophy and mild pulmonary hypertension. No improvement was observed despite antibiotic, steroid and diuretic therapy. She continued to require increasing levels of supplemental oxygen. The patient and her family decided not to pursue additional interventions and she passed away ten days after initial presentation.

**Results:** Idiopathic pulmonary fibrosis (IPF) is a chronic and often fatal interstitial lung disease that typically affects adults over the age of 60. The average survival from the time of diagnosis is between 3 and 5 years. There is significant heterogeneity among individual patients as the clinical course is both variable and unpredictable. Some patients have a protracted course with little functional impairment. In others, periods of relative stability can be punctuated by an acute respiratory worsening, characterized by worsening of symptoms, lung function, and/or radiographic appearance. Surgical and invasive procedures have been associated with the development of AE-IPF, but the precise triggers and mechanisms driving AE-IPF remain unknown.

**Conclusion:** While the management of AE-IPF involves the exclusion and treatment of alternate diagnoses, a lack of clinical improvement should prompt goals-of-care discussions and palliation. Further research is required to identify patients at risk for AE-IPF.
31-R  **Poster:** Obstructive Sleep Apnea Among Participants of Pittsburgh HIV Lung Cohort

**Presenter:** Maniraj Neupane, Resident

**Research Interest:** Clinical
   Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD, MS

**Funding Source:** NIH R01HL120398, K24HL123342, R01HL125049 (AM)

**Authors:** Maniraj Neupane MD, PhD, Cathy Kessinger RN, Deborah McMahon MD, Mehdi Nouraie MD, Rebecca DeSensi BA, Sanjay Patel MD, MS, Patrick Strollo MD, Alison Morris MD, MS

**Introduction:** Sleep disturbances including obstructive sleep apnea (OSA) are common with chronic inflammatory illness such as human immunodeficiency virus (HIV) infection. The aim of this study was to determine the risk factors of OSA in an HIV+ cohort.

**Methods:** HIV+ individuals identified at higher risk of OSA by Multivariable Apnea Prediction Questionnaires and their age, gender, and body mass index matched non-HIV+ controls were enrolled into this study. They underwent overnight limited channel sleep study using ApneaLink in the sleep lab. Demographic data, HIV treatment information, sleep questionnaires, comorbidities, and pulmonary function tests were recorded. The apnea hypopnea index (AHI) was calculated as the average number of episodes of apnea and hypopnea per hour of sleep. Oxygen desaturation index (ODI) was defined as the number of times per hour of sleep that oxyhemoglobin saturation dropped by more than 4% from baseline. Significant OSA was defined as an AHI of ≥15 events/hour. Participant characteristics were compared using Wilcoxon test for continuous and Fisher’s exact test for categorical variables. Univariate and multivariable logistic regression analyses were used to estimate the odds of OSA among those with HIV. Sensitivity analyses were performed using an AHI cut-off of ≥ 5. All analyses were performed using statistical software R.

**Results:** 57 participants (37 HIV-infected and 20 non-HIV+) between 25-70 years were enrolled, 68.4% were females. Almost half (49.1%) of the participants had BMI ≥30 kg/m2 and neck circumference ≥40cm. Median waist circumference was 105.9 cm (interquartile range 91.9-116.1). Prevalence of hypertension, cardiovascular disease, lung functions and airway disease were similar in both groups. Average AHI [median (interquartile range)] was lower in the HIV+ individuals 7.1 (4.7-15.4) than in the non-HIV+ 15.3 (6.3-20.8). Average ODI was lower in the HIV+ 6.1 (2.5-12) than the non-HIV+ 13.4 (4.2-18.7). 37.5% of the participants were found to have OSA, 29.7% among HIV+ compared to 52.6% in non-HIV+, p: 0.14. There was reduced odds of OSA among the HIV+ participants in both unadjusted (odds ratio: 0.38 (95% confidence interval 0.12-1.19) and adjusted (OR: 0.44; 95% CI 0.12-1.63) logistic regression analyses. Sensitivity analyses using an AHI=5 cut-off yielded similar results.

**Conclusion:** Risk assessment screening for OSA developed for non-HIV+ individuals may perform poorly in people who are HIV+, especially for moderate to severe OSA. Risk factors for OSA may be different in HIV+ individuals.
**32-R Poster:** Initial Results From a Newly Established Solid State SPECT Myocardial Flow Quantification Program

**Presenter:** Ricardo Nieves, Resident

**Research Interest:** Clinical Cardiology

**Mentors:** Prem Soman MD

**Authors:** Ricardo Nieves MD, Joseph Dietz CNMT, Prem Soman MD

**Introduction:** The inherent advantages of solid state detector technology have enabled dynamic SPECT imaging for myocardial blood flow (MBF) quantification. We report data from our first twelve months of experience with flow quantification with CZT SPECT.

**Methods:** Patients referred for vasodilator stress MPI were randomly selected for dynamic imaging on a DSPECT camera. The patient population was reflective of referral patterns for MPI or post-heart transplant (HT) evaluation. Patient positioning was accomplished with a hand-injected 1mCi Tc-99m sestamibi (MIBI) pre-scan. Vasodilator stress, and rest/stress MIBI injection using an automated syringe pump, were performed with the patient under the camera. The protocol consists of 9mCi and 30mCi of MIBI in 2ml saline followed by a 40 mL saline flush for the rest and stress studies, respectively, with the tracer injection performed 50s after Regadenoson stress. Data acquired in list mode were processed on the INVIA 4DM platform. Significant manual adjustments were made to the blood pool and tissue ROI positions for input and myocardial activity curve derivation.

**Results:** Of 104 non-transplant patients, 83 had normal MPI. Global myocardial flow reserve (MFR), peak stress flow (PSF) and rest flow (RF) were compared between patients with normal and abnormal MPI (2.17 vs 1.89, p = .16; 2.91 vs 1.91, p=.00; and 1.5 vs 1.1, p= .028, respectively). Among patients with normal MPI, MFR (2.1 vs 2.01, p=.287), PSF (3.1 vs 2.7, p=.044), and RF (1.6 vs 1.5, p=.48) were compared between men and women. Among 16 HT patients the RF was higher compared to non-transplant patients (1.8 vs 1.4, p=.032) while MF and PSF were similar.

**Conclusion:** Myocardial flow quantification with dynamic SPECT is feasible in the clinical setting and provides physiologically tenable values. Further studies are needed to evaluate its additive value to relative perfusion imaging.
**Poster: Distinct Myocardial Disease Patterns Detected on Free-Breathing Motion-Corrected Late Gadolinium Enhancement Associate with Baseline Disease Severity and Incident Outcomes in a Large Clinical Population**

**Presenter:** Hongyang Pi, Resident

**Research Interest:** Clinical Cardiology

**Mentors:** Erik Schelbert MD

**Authors:** Hongyang Pi MD, Fredrika Fröjd , Eric Olausson, Aatif Sayeed, Maren Maanja MD, Louise Niklasson, Timothy Wong MD, Martin Ugander MD, Hui Xue PhD, Peter Kellman PhD, Erik Schelbert MD

**Introduction:** Nearly all late gadolinium enhancement (LGE) literature employs breath holding which performs poorly in frail patients where disease is prevalent; but free breathing motion corrected LGE (mocoLGE) overcomes this limitation while providing similar (R2=0.96), unbiased quantitative myocardial infarction (MI) size measures on Bland-Altman plots. We thus hypothesized distinct patterns of myocardial disease specifically noted specifically on mocoLGE would associate with baseline disease severity measures and subsequent outcomes.

**Methods:** In 1822 consecutive patients referred for clinical cardiovascular magnetic resonance (CMR), we identified nonischemic scar (n=335), MI (n=337), or cardiac amyloidosis (CA, n=61) depicted by mocoLGE. Adjusting for several conventional clinical and demographic variables, we used multivariable: 1) linear regression models to identify associations with baseline a) B-type natriuretic peptide (BNP) and b) ejection fraction (EF), and 2) Cox Regression models to identify associations with incident hospitalization for heart failure and all-cause mortality.

**Results:** Nonischemic scar, MI and CA detected by mocoLGE associated with baseline disease severity and outcomes in multivariable models. Specifically, nonischemic scar (beta 0.279, se 0.069, p<0.001), MI (beta 0.346, se 0.081, p<0.001), and CA (beta 0.559, se 0.167, p<0.001) each associated with higher baseline log transformed BNP. Similarly, nonischemic scar (beta -3.37, se 0.61, p<0.001), MI (beta -7.93, se 0.68, p<0.001), and CA (beta -5.21, se 1.47, p<0.001) each associated with lower baseline EF. After 5.5 years follow-up (IQR 3.7-6.5 yrs), nonischemic scar (HR 1.34, 95%CI 1.05-1.71), MI (HR 1.38, 95%CI 1.05-1.80), and CA (HR 5.04 95%CI 3.41-7.45) each associated with outcomes.

**Conclusion:** Myocardial disease patterns detected by mocoLGE each associated with 1) baseline disease severity and 2) incident adverse events. These data from a large cohort, in addition to prior work, suggest robust detection of clinically relevant disease by free-breathing mocoLGE, supporting its clinical deployment.
34-R  **Poster:** Management of Pulmonary Arterial Hypertension in a Designated Comprehensive Care Center (CCC) Is Associated with Better Outcomes Compared to non-CCC Hospitals

**Presenter:** Hongyang Pi, Resident

**Research Interest:** Clinical Cardiology

**Mentors:** Stephen Chan MD

**Authors:** Hongyang Pi MD, Chad Kosanovich MD, Adam Handen MS, Michael Tao MD, Jacqueline Visina BS, Gabrielle Van Speybroeck MD, Stephen Chan MD

**Introduction:** Pulmonary arterial hypertension (PAH) is a rare but life-threatening disease characterized by progressive elevation of pulmonary arterial pressures. In the past two decades, there have been significant strides in targeted medical therapies that drastically improved the three-year survival from 48% to 84%. Despite these advances, there remains missed opportunities to improve outcomes in PAH with delayed diagnosis, misdiagnosis, and late or inappropriate implementation of treatment. As a result, current guidelines recommend PAH to be managed in expert centers where evidence-based diagnostic algorithms guide experienced physicians and support staff. However, there is insufficient evidence that implementation of these recommendations in a specialty center would improve the diagnostic workup or clinical outcomes in a PAH cohort.

**Methods:** This study used UPMC's electronic health record to extract patients meeting the inclusion criteria for PH (above 18 years of age, a diagnosis of PH by ICD 9 codes and at least one right heart catheterization (mean pulmonary arterial pressure greater than 25 mmHg). Hospitalizations and mortality were determined based on MARS record and Social Security Death Index. Overall individual endpoints (mortality and/or hospitalizations during the follow-up period) were described using Kaplan-Meier survival estimation and log-rank comparison tests or Cox proportional hazards modeling when appropriate.

**Results:** All the PH patients were classified into 5 groups based on guideline definition and physician documentation. A total of 2057 patients were included in the study and further stratified each class into two possible cohorts: those managed at the Pulmonary Hypertension Comprehensive Care Center (PH-CCC) patients or those managed outside this specialty care center. The clinical outcomes (all-cause mortality and hospitalization) of CCC vs. non-CCC patients were compared. Specifically for Group 1 PH/PAH patients, we compared the quality of care in PH-CCC and non-CCC hospitals: diagnostically, comparing the frequency of monitoring Right Heart Catheterization (RHC), Pulmonary Function Test (PFT), Ventilation/Perfusion scan (V/Q scan), sleep study, brain natriuretic peptide (BNP), Hepatic Function Test and 6 minute walk test (6MWT); and therapeutically, comparing the use of vasodilators (single vs combination of vasodilators; frequency of use of IV vasodilators).

**Conclusion:** This study describes the management of PAH in a large, real-world cohort of consecutive patients with long term follow-up. It also sheds light on the guideline recommendations of comprehensive care center for PH management. It can potentially shift the paradigm for PH referral and management.
**35-R  Poster:** Implications of Initial Recorded Rhythm on Cardioverter-Defibrillator Placement and All-Cause Mortality in Sudden Cardiac Arrest Survivors

**Presenter:** Vincenzo Polsinelli, Resident

**Research Interest:** Clinical Cardiology

**Mentors:** Samir Saba MD

**Authors:** Vincenzo Polsinelli MD, Norman Wang MD, Krishna Kancharla MD, Aditya Bhonsale MD, Sandeep Jain MD, Samir Saba MD

**Introduction:** Sudden cardiac arrest (SCA) rhythms have been traditionally divided into shockable (ventricular tachycardia (VT)/ventricular fibrillation (VF)) and non-shockable (asystole (ASY)/pulseless electrical activity (PEA)) rhythms. However, it remains unclear if the specific rhythm has implications on patient management and long-term mortality.

**Methods:** We evaluated the records of 1433 patients admitted to the hospitals of University of Pittsburgh Medical Center with SCA between 2000 and 2012 and discharged alive. Of those, 1123 patients had an identifiable initial SCA rhythm. Subjects included were >18 years of age, and without an ICD in place. Initial SCA rhythms were categorized as VT, VF, ASY, PEA. Differences in baseline characteristics among initial recorded rhythms were described using ANOVA for continuous variables, and χ² for discrete variables. Time to death comparisons were made using Cox-proportional hazards and survival functions between initially recorded rhythms and within each rhythm, between ICD recipients and nonrecipients. All survival functions were adjusted for differences in baseline characteristics.

**Results:** The 1123 SCA survivors had a mean age of 61.7±15.4, 440(39.2%) were women and 632(56.3%) suffered an in-hospital SCA. The study cohort was mostly white (932[83%]) with a high prevalence of coronary artery disease (750[66.8%]) and diabetes (356[31.7%]). Of the overall cohort, 355(31.6%) received an ICD and 493(43.9%) died over a mean follow-up of 3.76±3.23 years. Patients with VF (254[43.6%]) or VT (83[43.9%]) were more likely to receive ICD therapy compared to those with ASY (9[5.3%]) or PEA (9[4.8%]) (P<0.001). All-cause mortality was lower in VF compared to the other groups (P<0.0001). ICD therapy was associated with lower risk of death in the VF group (HR:0.61[0.45–0.83];P=0.002). There were non-significant associations toward less mortality with the ICD in patients with VT (HR:0.64[0.40–1.03];P=0.066) and ASY (HR:0.39[0.12–1.31];P=0.128) but not in those with PEA (HR:0.93[0.39–2.23];P=0.876).

**Conclusion:** Long-term survival in post-SCA subjects is associated with initial SCA rhythm. Although SCA survivors with shockable rhythms were more likely to receive ICDs, the ICD was associated with lower risk of death in all patients except those presenting with PEA. Our data suggest that a more detailed SCA rhythm classification has important implications to patient management and long-term survival.
**Poster: Oral Cytokine Expression is Linked to Oral HIV-1 Levels in ACTG A5254**

**Presenter:** Joseph Rocco, Resident

**Research Interest:**
- Clinical General Internal Medicine

**Mentors:** Bernard Macatangay MD

**Funding Source:** ACTG

**Authors:** Joseph Rocco MD, Zachary York MD, Janet McLaughlin, Luann Borowski, Jennifer Webster-Cyriaque PhD, Caroline Shiboski PhD, Judith Aberg MD, Charles Rinaldo PhD, Bernard Macatangay MD

**Introduction:** HIV infection is known to disrupt oral mucosal immunity, but the pathogenesis of this immune dysregulation remains unknown. We determined the levels of 11 soluble immune mediators in oral washings of people with HIV (PWH) with varying levels of plasma viremia and CD4+ T cell counts. We also evaluated whether these immune mediators are associated with levels of HIV in blood and oral washings with the aim of characterizing the mucosal immune response at variable stages of HIV infection.

**Methods:** Oral washings were obtained from participants of ACTG A5254, a cross-sectional study of PWH to evaluate oral complications of HIV. Participants were divided into 4 strata: A (n=148; 52% on ART), CD4=200 cells/mm3, plasma HIV-1 RNA (VL)>1000 cps/mL; B (n=82; 98% on ART), CD4=200, VL=1000; C (n=29; 21% on ART), CD4>200, VL>1000; D (n=29; 100% on ART), CD4>200, VL=1000. Levels of soluble markers were tested in oral washings using a multi-bead fluorescent platform, and were compared between strata. Associations between soluble marker levels and HIV in plasma and oral washings as well as CD4+ counts were determined.

**Results:** Stratum (St) A participants (CD4 <200, VL >1000) had higher levels of pro-inflammatory markers IL-6, IL-17, TNFa, IL-1ß, and IFN? compared to St B and St D which had VL<1000 and where 98-100% of participants were on ART (p=0.02 to p<0.0001; Kruskal-Wallis with Dunn’s post-test, adjusted for multiple comparisons), but were not different from St C. Two pro-inflammatory markers, IL-12p70 and IL-8, and the anti-inflammatory marker IL-10 differentiated St A from the other 3 strata (p=0.046 to p<0.0001). St B and D had no differences in levels of the soluble markers except for IFN? (p=0.04). Oral HIV levels correlated with plasma HIV (r=0.76; p<0.0001, Spearman) and with IL-6, IL-16, IL-8, TNFa, IFN?, and IL-10 (all r>0.4; p<0.001). Meanwhile, plasma VL only correlated with TNFa, IFN?, and IL-10 (all r>0.4; p<0.001). No correlations were seen with IL-2, and only modest (r<0.35) correlations were seen with IL-17. No significant correlations were observed with CD4 count.

**Conclusion:** Our results suggest that high levels of oral HIV rather than low CD4 counts or plasma HIV are more linked to production of oral immune mediators. Despite severe immunosuppression, participants with AIDS demonstrated elevated levels of cytokines corresponding to both Th1 and Th2 T cell responses. The interplay of HIV and these immune mediators could be an important factor in the oral health of PWH.
**Poster: Frailty Tested By Gait Speed Is a Risk Factor for Liver Transplant Respiratory Complications**

**Presenter:** Tariq Salim, Resident

**Research Interest:** Clinical General Internal Medicine

**Mentors:** Michael Dunn MD

**Authors:** Tariq Salim MD, Leah Nestlerode BS, Erin Lucatorto BS, Tamara Wasserman BS, Hassieb Din MD, Yaming Li PhD, Douglas Landsittel PhD, Amit Tevar MD, Jonas Johnson MD, Michael Dunn MD

**Introduction:** Frailty and sarcopenia are known risk factors for liver transplant death and complications. While weakness of airway/respiratory muscles likely underlies the respiratory complications of transplantation—aspiration, pulmonary infection, prolonged intubation—little is known about whether measuring frailty or sarcopenia could identify risk for these frequent, serious respiratory-specific adverse events.

**Methods:** For 107 patients (74 men, 33 women) transplanted in 1 year, we measured frailty with gait speed, chairstands, and Karnofsky Performance Scale (KPS), and sarcopenia with skeletal muscle index (SMI) on CT at L3 using published pretransplant cutoffs. We recorded stress tested cardiac work as double product (DP). Outcomes included days of postoperative intubation, evidence of aspiration on imaging, clinically evident pneumonia, need for reintubation/tracheostomy, days to discharge, and survival. We tested association of variables with outcomes using linear and logistic regression for continuous and binary outcomes respectively, adjusted for age, sex and MELD-Na.

**Results:** Associations of pretransplant testing with outcomes are shown in the Table. For the outcome of days of postoperative intubation (0.79 ± 2.13d), both gait speed (1.01 ± 0.30m/s) and KPS (80 ± 15%) were significantly associated with shorter intubation time; data were log transformed for linearity of analysis. In 28 patients with imaging evidence of aspiration, gait speed was negatively associated with aspiration and KPS showed a similar but nonsignificant trend. In 33 patients with clinically evident pneumonia, gait speed again was negatively associated and DP (17,500 ± 6400) showed a nonsignificant negative trend. No pretransplant test was associated with length of stay or need for reintubation or tracheostomy (14 patients). The 4 patients who died were too few for analysis. Sarcopenia (<50 cm²/m² in men, < 39 cm²/m² in women, 38% of patients), was not associated with adverse respiratory outcomes. Significance of the negative association of gait speed with intubation time, aspiration and pneumonia and of KPS with intubation time persisted in models adjusted for age, sex and MELD-Na scores.

**Conclusion:** We found that decreased gait speed, a common index of general frailty, indicates significant risk for post-transplant respiratory complications. Whether more specific testing of respiratory muscle or oropharyngeal function could refine such risk assessment may merit exploration.
38-R **Poster:** Big Data Analytics Identifies Ulcerative Colitis Patients at Increased Risk for Incident Colorectal Neoplasia Using Multiyear Patterns of Routine Clinical Lab Values

**Presenter:** Carlita Shen, Resident

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

**Mentors:** David Binion MD

**Authors:** Carlita Shen MD, Claudia Ramos Rivers MD, Dmitriy Babichenko MD, Douglas Hartman MD, Ioannis Koutoubakis MD, Marc Schwartz MD, Siobhan Proksell MD, Elyse Johnston MD, Jana Hashash MD, Arthur Barrie MD, Janet Harrison MD, Gong Tang MD, Andrew Watson MD, David Binion MD

**Introduction:** Patients with ulcerative colitis (UC) are at increased risk for development of colorectal dysplasia and/or cancer (colorectal neoplasia/CRN). Factors associated with the development of UC related CRN include family history, presence of primary sclerosing cholangitis, disease duration and inflammatory activity. Inflammatory activity varies in UC across the years of illness, and may be reflected in alterations in routine laboratory values including rise in C reactive protein or fall in albumin. These biomarkers are readily accessible in the electronic medical record. There is limited data regarding the use of patterns of inflammatory biomarkers as a tool to identify patients at increased risk of CRN, who would benefit from screening.

**Methods:** We performed an 8-year longitudinal analysis (2009-2016) of demographic, clinical, laboratory, and treatment data from a prospective IBD natural history registry to investigate inflammatory markers in patients with UC and their relationship with emergence of CRN. Patients diagnosed with incident CRN were identified using computer searches and manual review of pathology data. The Glasgow score is based on CRP and albumin values (0: both normal, 1: one abnormal, 2: both abnormal) and was calculated each year prior to CRN diagnosis. Patients were then grouped into all normal, some abnormal, and all abnormal Glasgow score categories.

**Results:** A total of 1064 patients with UC (median age 43.9 (QR 34.1-56.9), 44% women) were included in the analysis. 93 UC patients were identified with incident CRN and 40 patients with complete laboratory data formed the study population. These individuals had combinations of the following lesions (low grade dysplasia 24, indefinite 17, high grade dysplasia 1, colorectal cancer 6). Of those patients with CRN, 15% had ASA exposure, 38% had anti-TNF exposure, 55% had immunomodulator exposure, and 55% had steroid exposure. Patients with UC and CRN had significantly higher median sedimentation rate (ESR; P=0.001) and lower albumin (P<0.001). The prevalence of some abnormal or all abnormal annual Glasgow score patterns was significantly higher in the CRN group compared with individuals who did not develop CRN (P = 0.001).

**Conclusion:** Metadata generated from routine laboratories can help identify individuals at increased risk of developing CRN in UC. The presence of abnormal Glasgow scores using inflammatory markers is associated with increased risk of incident dysplasia in UC patients. On the basis of this data, we propose incorporation of inflammatory markers including the CRP-albumin score to identify high risk UC patients for more stringent CRN surveillance and intervention.
**Introduction:** Chronic obstructive pulmonary disease (COPD) has been proposed to be a disease of accelerated aging. Coronary artery calcifications, which associate with age, are increased in patients with COPD and linked to poor outcomes and increased mortality. However, little data exists regarding the relationship between thoracic aorta calcifications (TACs), aging, and disease outcomes in COPD. We hypothesized that TACs are associated with worse lung function, increased symptoms, and reduced exercise capacity in current and former smokers.

**Methods:** Participants from the University of Pittsburgh SCCOR cohort (N=285) underwent pulmonary function testing, chest CT imaging, dyspnea assessment, (mMRC dyspnea tool), and incremental shuttle walk testing. The thoracic aorta from the level of the carina through the descending aorta at the level of the diaphragm was manually outlined on CT with the use of proprietary software. TACs were quantified using the volume of voxels within the outlined thoracic aorta with pixel values > 130HU. The associations between TACs and age, FEV1%, and incremental shuttle walk distance were assessed by robust linear regression with and without adjustment for covariates. Association of quartiles of TACs with significant dyspnea, (MMRC = 2) was evaluated with logistic regression with and without adjustment for covariates. Association of quartiles of TACs with significant dyspnea, (MMRC = 2) was evaluated with logistic regression with and without adjustment for covariates. Lung function and quantitative emphysema were not associated with TACs.

**Results:** Participants were a median age of 64 (IQR =56-72), 51% male (n=147) and had a median FEV1% predicted at enrollment of 89% (IQR = 64-114.4%). Only 11.2% (n=32) of participants reported significant dyspnea. Volume of TACs was positively associated with age (R2 = 0.21, p < 0.001) and number of pack years smoked (R2 = 0.03, p < 0.001). The 50th - 75th and 75th - 100th percentiles of TACs were significantly associated with the presence of symptoms in unadjusted (OR 5.96, 95% CI 1.27-27.99; OR 7.22, 95% CI 1.58-33.07, respectively) and adjusted (age, gender, and obstruction severity) analyses. Volume of TACs was positively associated with walk distance in univariate analysis (?=27.0, p < 0.001) and when adjusted for age, gender, obstruction severity, and symptoms, (?=10.6, p=0.009). This independent association remained significant after the addition of quantified coronary artery calcifications to the model (?=-11.2, p=0.005). Lung function and quantitative emphysema were not associated with TACs.

**Conclusion:** TACs are independently associated with symptom burden and exercise capacity in smokers even after consideration of age, lung function and coronary artery calcification. These data suggest that TACs may be markers of comorbid disease or frailty in smokers.
**Poster: Association of Depressive Symptoms with Systemic Inflammation in Patients with COPD**

**Presenter:** Hilary Strollo, Resident

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Frank Sciurba MD

**Funding Source:** NIH-NHLBI; SCCOR: P50 HL084948; COPDGene: U01 HL08

**Authors:** Hilary Strollo DO, Chad Karoleski BS, Nicholas Hanania MD, Russell Bowler MD, Syed Nouraie MD, Craig Riley MD, Jessica Bon MD, Frank Sciurba MD

**Introduction:** Depression is a prevalent comorbidity of chronic obstructive pulmonary disease (COPD) and is associated with poor outcomes and increased mortality. While both COPD and depression have been independently associated with systemic inflammation, this finding has not been validated in a large COPD cohort.

**Methods:** Individuals from the University of Pittsburgh SCCOR cohort and the COPDGene cohort with spirometric airway obstruction (FEV1/FVC < 0.7) were evaluated using the Beck Depression Inventory (BDI) (depressive symptoms defined = 10) and the Hospital Anxiety and Depression Scale (HADS) (depressive symptoms defined = 8), respectively. Participants completed the Saint George’s Respiratory Questionnaire (SGRQ) and UCSD Shortness of Breath Questionnaire (UCSD SOBQ). Plasma IL-6 was measured using ELISA. T-test, univariate and multivariate analyses and chi-square analysis (stratified by top SD of log IL-6 and depression score) were performed to identify determinants of depression.

**Results:** Participants in the SCCOR cohort (N=220) included: 123 males (24 with depressive symptoms), 97 females (23 with depressive symptoms), age 67 ± 7, BMI 27.5 ± 4.1 kg/m2, current smokers (93). GOLD distribution included GOLD 1 (30.5%), GOLD 2 (55.0%), GOLD 3 (13.2%), GOLD 4 (1.3%). Participants in the COPDGene cohort (N=745) included: 420 males (61 depressive symptoms, 325 females (36 depressive symptoms), age 69 ± 8, BMI 26.2 ± 4.1 kg/m2, GOLD distribution included GOLD 1 (22.7%), GOLD 2 (40.9%), GOLD 3 (25.5%), GOLD 4 (10.9%). Univariate analysis demonstrated elevated BDI and HADS scores were significantly associated with log IL-6, SGRQ Total and current smoking status in both SCCOR and COPDGene cohorts. Additionally, age, FEV1 % predicted and 6-minute walk distance were significantly associated with elevated HADS score (Table 1). A stepwise regression and chi-squared analysis showed that log IL-6 independently correlated with depression in obstructed individuals in both SCCOR (p=0.012, X2 p=0.07) and COPDGene (p?0.001, X2 p = 0.001).

**Conclusion:** Data from both cohorts demonstrate that patients with COPD and depressive symptoms have elevated plasma IL-6 at baseline independent of % predicted FEV1. Our results suggest that systemic inflammation may play a significant and possibly bidirectional role in depression associated with COPD.
Poster: Retrospective Review of Anticoagulant Use in Brain Tumor Patients

Presenter: Andrew Swartz, Resident

Research Interest: Clinical
Hematology/Oncology

Mentors: Jan Drappatz MD

Authors: Andrew Swartz MD

Introduction: Neuro-oncology patients, like all cancer patients, are at high risk for venous thromboembolic complications and frequently require anticoagulation. For example, 30% of GBM patients will develop VTE over the course of their illness. LMWH has become favored over warfarin in cancer patients with VTE as it was found to have better efficacy in preventing recurrent VTE and no significant difference in bleeding risk. LMWH also has more predictable pharmokinetics, does not require lab monitoring, and has rapid onset with predictable clearance. Although the CLOT trial in NEJM provided evidence for superior efficacy of LMWH in cancer patients with VTE, the study had a small sample of patients with brain cancer. There are, in fact, no randomized trials that have directly compared LMWH with warfarin specifically in patients with brain tumors. Additionally, patient adherence continues to be an issue with LMWH as it requires injection. Novel oral anticoagulants (NOACs) have emerged as a treatment for cancer associated VTE with comparable safety and efficacy to LMWH. NOACs have added benefit over LMWH in that they do not require injection and reduce patient burden. Although NOACs are being used more and more frequently in cancer patients, there remains little data to support their use in patients with primary and metastatic brain tumors.

Methods: Study Design: Retrospective study Setting/Participants: Reviewed medical records of approximately 200 patients at UPMC Hillman Cancer Center between 2015 and 2018. Patients with primary and metastatic brain tumors on anticoagulation. Measurements: Underlying cancer diagnosis, name of anticoagulant agent, duration of anticoagulation treatment, age and sex of patients, recurrent VTE on treatment, bleeding complications while on treatment.

Results: Preliminary Data-Patient’s pooled: 62% of patient’s had GBM, 18% had CNS lymphoma, 6% had metastatic brain tumors, 6% had anaplastic astrocytoma, 4% had glioma, 2% had oligodendroglioma, 2% had meningioma-AC indication: 90% on AC for DVT/PE, 8% a.fib/a.flutter, 2% FVL mutation-Type of anticoagulation: 61% were on Lovenox, 30% were on NOAC (eliquis or xarelto), 9% were on warfarin-Major Bleeding episodes: 10 instances in patient pool. Of those patients, 7 were on lovenox, 2 were on warfarin, 1 was on Xarelto.-Minor Bleeding: 5 instances in patient pool, 4 were on lovenox, 1 was on eliquis.

Conclusion: DOACs such as Xarelto and Eliquis are not associated with increased risk of major or minor bleeding in brain tumor patients.-Lovenox continues to be the preferred choice for anticoagulation in brain tumor patients.
**Poster: Low IgG2 Level and Increased Risk of Infections in Lung Transplant Recipients**

**Presenter:** Maylene Xie, Resident

**Research Interest:** Clinical General Internal Medicine

**Mentors:** Andrej Petrov MD

**Funding Source:** CSL Behring

**Authors:** Maylene Xie MD, Russell Traister MD, Kara Coffey MD, Joseph Pilewski MD, Andrej Petrov MD

**Introduction:** Our previous study has demonstrated that lung transplant (LT) recipients with severe hypogammaglobulinemia (HGG) are at increased risk for recurrent pneumonias and more antibiotic courses at 1-year post-transplant. The significance of IgG subclass deficiency has not yet been examined in the LT population.

**Methods:** IgG subclass levels were measured before LT in a single-center prospective observational study and related to 1-year post-transplant infectious outcomes and survival. Analysis was performed using non-parametric tests.

**Results:** 116 LT recipients were evaluated. The median age at transplant was 56.8 years, 62.2% of subjects were males, and 91.8% were Caucasian. 35% of subjects had idiopathic pulmonary fibrosis (IPF) and 32% had chronic obstructive pulmonary disease (COPD). Low IgG2 subclass level was associated with low pre-transplant pneumococcal titers (p = 0.005) as well as an increased incidence of pneumonias (p = 0.001) and decreased survival (p=0.014). The total number of pneumonias, two or more pneumonias, and the number of days with pneumonia were also related to low IgG2 level (p = 0.0008 for all values). Low IgG2 subclass level was associated with a higher number of post-transplant hospital days (p = 0.01) and ICU days (p = 0.052). IgG subclass levels were not related to the type of induction agent, post-transplant immunosuppression regimen or lymphocyte levels.

**Conclusion:** Low pre-transplant IgG2 subclass level may represent an important novel immunologic biomarker in lung transplantation due to its association with increased pneumonias and decreased survival at 1-year post-transplant. The mechanism of these findings will need be studied further.
**Introduction:** Idiopathic pulmonary fibrosis (IPF) is a progressive and disabling disease with an unpredictable clinical course. In addition to multidisciplinary management focused on oxygen therapy, rehabilitation, and potential transplant evaluation, this disease requires emphasis on patient and caregiver education and support. Support groups (SG) serve as a venue for IPF education, communication, and empowerment. Since 2001, our specialty referral center has sponsored monthly voluntary SG meetings focused on disease understanding, emotional well-being, oxygen therapy management, and advanced care planning, among others. While recent studies have reported benefits of SG programs in this population, the impact of SG participation on palliative care (PC) referral and end-of-life discussions remain unclear.

**Methods:** This was a single center retrospective cohort study of IPF patients evaluated at our specialty referral center for the first time between 2000 and 2016 (n=828). Exclusion criteria included lung transplant recipients and those who did not have IPF. All patients were invited to participate in voluntary monthly SG meetings held at our affiliated university. Participation was defined as attendance in ≥1 SG meetings. PC was defined as a formal request for consultation in the health system repository.

**Results:** One hundred seventy-eight (22%) IPF patients participated in ≥1 SG meetings. Compared with IPF patients who did not attend SG, participants were younger at diagnosis (68y v. 70y, p=0.005), resided closer to our institution (31mi v. 54mi, p=0.003), and had more outpatient visits (9 v. 3, p<0.001). This cohort had less severe baseline lung disease, as measured by forced vital capacity (FVC%), diffusing capacity of lungs for carbon monoxide (DLco%), Gender, Age, and Physiology (GAP) Index, and oxygen requirement. SG participation resulted in higher frequency of PC referral (35% v. 19%, p<0.001) and lower mortality (HR 0.59, 95% CI 0.40-0.86, p=0.006) after adjusting for prognostic factors, including sex, initial GAP Index and oxygen requirement, and number of outpatient visits.

**Conclusion:** IPF is an unrelenting disease that demands multidisciplinary care for patients and their caregivers. SG participation was associated with higher frequency of PC referral and lower mortality compared to IPF patients who did not attending meetings. Participants resided closer to our institution and had more outpatient visits, suggesting possible correlations between more active patient-provider engagement and comfort with introducing end-of-life discussions. Future studies will aim to involve IPF patients with more severe baseline lung disease and assess the impact of SG on health-related quality of life.
**48-R Poster:** Pulmonary Function and Cognitive Impairment in Persons Living with Human Immunodeficiency Virus Infection: A Pilot, Cross-Sectional Study

**Presenter:** Yoseob Joseph Hwang, Resident

**Research Interest:** Epidemiology
General Internal Medicine

**Mentors:** Alison Morris MD

**Authors:** Yoseob Joseph Hwang MD, Seyed Mehdi Nouraie MD, Cathy Kessinger RN, Deborah McMahon MD, James Becker PhD, Alison Morris MD

**Introduction:** Persons living with HIV (PLWH) are at an increased risk of chronic obstructive pulmonary disease (COPD). Reduced pulmonary function has been recognized as a risk factor for developing cognitive impairment. Among PLWH, cognitive impairment presents a significant comorbid burden even in the era of antiretroviral therapy (ART). Therefore, we aimed to evaluate the relationship between pulmonary function and cognitive impairment in PLWH.

**Methods:** We performed a pilot, cross-sectional analysis of 36 PLWH who underwent Montreal Cognitive Assessment (MoCA) and pulmonary function testing between 2015 and 2016. We considered those with a MoCA score <24 to be cognitively impaired. Post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV1/FVC) <0.7 defined the presence of irreversible airway obstruction. Post-bronchodilator FEV1 <80% predicted represented a moderate severity of airflow limitation. Information on viral load, CD4 count, and receipt of ART were also obtained. We used multivariable penalized logistic regression to estimate the association between the measures of pulmonary function (post-bronchodilator FEV1/FVC and FEV1) and MoCA score.

**Results:** Participants had a mean of age of 52, with the majority identified as male (69.4%) and African-American (66.7%). Viral load was detectable in 29.4%, and median (interquartile range) CD4 count was 643 (344–911) cells/µL. Ninety-seven percent were prescribed ART. Cognitive impairment was prevalent, with 11 (30.6%) individuals having MoCA score <24. Age, sex, race, viral load, CD4 count, ART use, and comorbid conditions, such as cerebrovascular accident and obstructive sleep apnea, were not significantly different (all p>0.05) between individuals with MoCA score <24 and those with MoCA score =24. Both post-bronchodilator FEV1/FVC <0.7 (odds ratio, 0.75; 95% confidence interval, 0.08–6.99; p=0.80) and FEV1 <80% predicted (odds ratio, 1.13; 95% confidence interval, 0.23–5.66; p=0.88) were not associated with MoCA score <24.

**Conclusion:** In this small cohort of PLWH, there did not appear to be an association between reduced pulmonary function, specifically irreversible airway obstruction, and the degree of cognitive impairment identified by MoCA score <24. Analysis of a larger cohort of PLWH with more comprehensive cognitive tests is warranted to better characterize the relationship between pulmonary function and cognitive impairment.
**49-R Poster:** Differences in Readmission Rates of Patients Admitted for Acute Decompensated Heart Failure to Internal Medicine and Cardiology Services

**Presenter:** Casey McQuade, Resident

**Research Interest:** Epidemiology
General Internal Medicine

**Mentors:** Gavin Hickey MD

**Authors:** Casey McQuade MD, Jennifer Prince BS, Alex Sommerfeld MD, Suresh Mulukutla MD, Gavin Hickey MD

**Introduction:** Heart failure readmission remains a problem of interest for general internal medicine (GIM) and cardiology practitioners alike. Specialty related differences in readmission and mortality rates have previously been described, but their causes have not been elucidated.

**Methods:** We retrospectively examined consecutive patients admitted for acute decompensated heart failure to GIM and cardiology services between September 1, 2014 and February 1, 2018. Discharge diagnosis was verified using ICD codes and chart adjudication by two reviewers. Patient comorbidities, clinical and laboratory markers of decongestion (decreased weight, increased BUN, increased creatinine, increased hematocrit), and cardiology clinic follow-up attendance were abstracted. The primary endpoints were all-cause readmission and all-cause mortality at 30 and 90 days. Multivariable Cox proportional hazards regression was used to assess the relationship between the primary outcomes and the collected data.

**Results:** A total of 738 individual patients over 1166 encounters were reviewed. Patients were 73±11 years old, more frequently Caucasian (79±4%), and male (98±1%). GIM admissions accounted for 637 encounters, with cardiology accounting for 529. GIM patients on average had a higher left ventricular ejection fraction (43%, vs. 38%, p<0.001). Length of stay (6.4 vs. 6.5 days, p=0.89) and patient complexity (Charlson comorbidity index, 6.0 vs. 6.1, p=0.88) were similar between specialties. Patients admitted to GIM were at higher risk of readmission (HR 1.28, 95% CI 1.07-1.53, p=0.006) and mortality (HR 1.36, 90% CI 1.09-1.69, p=0.007). On average cardiology patients lost a larger percentage of body weight (-6.1% vs. -5.5%, p=0.02) and more frequently experienced an increased BUN during admission (66% vs. 55%, p<0.001). Of the markers of decongestion analyzed, only increased BUN was associated with reduced mortality (HR 0.74, 95% CI 0.58-0.94, p=0.02) while none reduced readmissions. Outpatient cardiology follow-up attendance was significantly higher among cardiology patients at 30 days (31% vs. 24%, p<0.001) and was a protective factor for both readmission (HR 0.66, 95% CI 0.55-0.79, p<0.001) and mortality (HR 0.48, 95% CI 0.37-0.61, p<0.001).

**Conclusion:** Admission to a cardiology service for acute heart failure is associated with less risk of readmission and mortality. There were no significant differences in service characteristics to explain the differences in outcomes. Our results suggest that differences in post-discharge follow-up and not effective inpatient diuresis are most closely related to the differences in outcomes between the two services. Future quality improvement efforts should focus on increasing rates of post-discharge follow-up for all acute heart failure patients to decrease readmission rates.
Poster: Reference Lung Values for Nepalese Population Residing at Wide Range of Altitudes

Presenter: Maniraj Neupane, Resident

Research Interest: Epidemiology
General Internal Medicine

Mentors: Annalisa Cogo MD

Funding Source: Ev-K2-CNR grant (MN, AC)

Authors: Maniraj Neupane MD, PhD, Annalisa Cogo MD, Delan Devakumar PhD, Om Kurmi PhD, Eva Rehfues PhD, Buddha Basnyat MD, Rainald Fischer MD, Jon Ayres MD, Philip Quanjer MD

Introduction: Reference values obtained from healthy subjects of similar age, height, sex and ethnicity are essential for interpreting spirometry results. However, there are no reference lung values applicable to Nepalese population permanently inhabiting from 59m to 5000m altitude. We aimed to check the applicability of Global Lungs Initiative (GLI2012) equations among the Nepalese population and derive appropriate ones if they did not fit. We also studied ethnic differences in pulmonary function and association with altitude of residence and malnutrition.

Methods: Individual spirometry data from 7-84 years asymptomatic non-smokers (N=2324, 58% females) were collected from participants of four separate studies conducted in different parts of Nepal. Castes were grouped post hoc as Sherpas (highlander), Mongols and remaining (lowlander) Nepalese. Forced expiratory volume (FEV1), forced vital capacity (FVC) and FEV1/FVC were compared to the GLI2012 predicted values and analyzed as a function of age and height using the lambda-mu-sigma method with ethnic group, altitude, body mass index and exposure to biomass smoke as explanatory variables.

Results: Participants’ primary residence ranged from low plains to mid hills and the Northern Himalayas, with 16.2% of analysed participants residing at >2500m altitude. Majority (~58%) of the participants used firewood for cooking. Lung function varied with altitude, which correlated with ethnicity. Lung indices in Sherpas were comparable to those in Whites while Mongols had values in between Sherpas and the Whites. Lowlander Nepalese of mixed ethnicity had 24.7% and 11.8% lower FEV1; 21.9% and 10.6% lower FVC than Sherpas and Mongols respectively. FEV1/FVC in lowlanders was below GLI predicted values (mean z-score -0.24, confidence interval -0.39;-0.18 in males, mean -0.43, CI -0.49;-0.37 in females) for Whites. Malnourished (44.4% girls; 48.5% boys) 7-18-year-old children had up to 21% smaller lung volumes than well-nourished peers.

Conclusion: Ethnic differences in lung function among Nepalese preclude the use of a single GLI correction factor thus we derived ethnic specific all-age lung reference values for Nepalese.
**Poster: Gender Differences in Glycemic Control, Microvascular and Macrovascular Complications in Hospitalized Patients with Diabetes**

**Presenter:** Neeti Patel, Resident

**Research Interest:** Epidemiology
Endocrinology and Metabolism

**Mentors:** Mary Korytkowski MD

**Funding Source:** Division of Endocrinology

**Authors:** Neeti Patel MD, Diana Pinkhasova MD, Janya Swami MD, Amy Donihi PharmD, Linda Siminerio PhD, Esra Karslioglu-French MD, Kristin Delisi CRNP, Deborah Hlasnik CRNP, Li Wang MS, Mary Kortykowski MD

**Introduction:** Gender differences have been described for glycemic control and prevalence of diabetes (DM) related complications in the outpatient setting but have not been examined in the hospitalized population.

**Methods:** To address this, we investigated gender differences in demographics, reasons for admission, glycemic control and variability (GV), macrovascular and microvascular complications, and length of stay in non-critically ill hospitalized patients with a secondary diagnosis of diabetes recruited for the Readmission and Comprehension of Diabetes Education at Discharge (ReCoDED) Study.

**Results:** To date, 111 men and 87 women have been recruited, with the majority having type 2 DM (86 vs. 79%). Participants age (men vs. women) was 60.6 ± 11.7 vs. 57.6 ± 11.8 years, BMI 32.2 ± 8.4 vs. 32.1 ± 10.6 kg/m2, systolic (SBP) 136 ± 26 vs. 127 mmHg ± 23 mmHg, diastolic (DBP) 77 ± 13 vs. 75 ± 14 mmHg, HbA1c 8.0 ± 2.3 vs. 8.3% ± 2.5%, and DM duration 14.5 ± 10.4 vs. 14.1 ± 11.6 years. The racial distribution, education level, employment status were similar. Men had more retinopathy (23 vs. 16%) and nephropathy (40 vs. 28%), but not neuropathy (60 vs. 63%). Women had a lower prevalence of coronary artery disease (49 vs. 36%), but a similar prevalence of CHF (37 vs. 37%), stroke (15 vs. 18%), and PVD (18 vs. 17%). The most frequent admission diagnoses were CVD (37 vs. 22%) and infection (10 vs. 19%). Mean blood glucose (BG) (198 ± 51 vs. 200 ± 54 mg/dl), GV (177 ± 80 vs. 182 ± 112 mg/dl), frequency of hypoglycemia (BG < 70 mg/dl) and hyperglycemia (BG >250 mg/dl) were similar in the 48 hours prior to discharge. Length of stay was 7.8 ± 6.9 vs. 8.3 ± 7.4 days.

**Conclusion:** In summary, this gender based description of glycemic control and prevalence of diabetes-related complications in an inpatient population demonstrates that hospitalized women with DM have fewer microvascular complications, a lower prevalence of CAD but a similar prevalence of CHF, stroke and PVD when compared to men, despite similar BMI and DM duration. The impact of these findings will be examined as a risk factor for hospital readmissions in this ongoing study.
Poster: Obstructive Sleep Apnea Does Not Increase Risk of Venous Thromboembolism

Presenter: Aman Rathore, Resident

Research Interest: Epidemiology
Pulmonary, Allergy and Critical Care Medicine

Mentors: Sanjay Patel MD

Funding Source: k24 HL127307

Authors: Aman Rathore MD, Michael Genuardi MD, Rachel Ogilvie PhD, Jared Magnani MD, Sanjay Patel MD

Introduction: Recent data from two large population-based studies suggests that OSA is associated with increased risk of venous thromboembolism (VTE). However, those studies relied on administrative data and did not account for obesity, a known VTE risk factor. We aimed to investigate whether OSA is an independent risk factor after accounting for obesity in a large clinical cohort.

Methods: We retrospectively examined the medical records of 42,191 patients undergoing diagnostic in-lab polysomnography at one of six University of Pittsburgh Medical Center (UPMC) sleep labs from 3/1999 to 12/2017. We excluded patients <18 years old, with history of malignancy, or with prior VTE at the time of baseline polysomnography, leaving 29,734 patients for analysis. The apnea hypopnea index (AHI) scored based on 10 seconds of absent airflow or >30% reduction in airflow accompanied by 4% desaturation, obtained from polysomnography reports. OSA severity was classified as none (AHI < 5 events/hr), mild (AHI 5-15 events/hr), moderate (AHI 15-30 events/hr), or severe (AHI > 30 events/hr). Incident VTE, defined as first diagnosis of pulmonary embolism or deep vein thrombosis, was identified using inpatient and outpatient ICD-9-CM or ICD-10-CM codes. Patient demographics and body mass index (BMI) were collected from polysomnogram reports. Cox proportional hazards regression models were created to examine the relation between AHI and VTE incidence.

Results: The cohort had a mean age of 50.0±14.4 yrs; 50.7% were men, and mean BMI was 34.5±8.8 kg/m2. The mean AHI was 21.8±26.9 events/hr with 30.4% no OSA, 27.3% mild OSA, 17.7% moderate OSA, and 24.6% severe OSA. After median follow-up time of 5.5 years, 1656 (5.6%) of patients had incident VTE. After adjusting for age and sex, each 10-unit increase in AHI was associated with a 1.04-fold (95% CI: 1.02-1.05) higher risk of incident VTE and those with severe OSA had 1.29-fold (95% CI: 1.12-1.49) higher risk compared to those without OSA. However, after additionally adjusting for BMI, no relationship remained between OSA severity and VTE risk with HR 1.00 (95% CI: 0.99-1.02) for every 10-unit increase in AHI and HR 1.00 (95% CI: 0.86-1.16) for severe vs. no OSA.

Conclusion: After accounting for obesity, OSA was not an independent risk factor for incident VTE in a clinical cohort. Our results suggest that estimates of the causal effect of OSA on VTE risk must account for obesity.
Poster: The Added Financial Burden of Price Increases of Already Established Antineoplastic Agents

Presenter: Michail Alevizakos

Research Interest: Health Services
Hematology/Oncology

Authors: Michail Alevizakos MD, Apostolos Gaitanidis MD

Introduction: Antineoplastic medication prices are overall increasing yet this phenomenon is not limited to new medications but can also be observed in already established medications.

Methods: We accessed the yearly payment files from Medicare Part B for injectable antineoplastic medications (codes J8501-J9999) for the years 2010-2017 and all costs were adjusted to 2017 USD to adjust for inflation. We then calculated price-per-dose for every medication that was available at least a year prior and compared that price with the price-per-dose that the medication would have if it was only affected by inflation. We then multiplied the difference with the total doses of the medication administered in order to calculate the additional cost accrued by Medicare from medications whose price had increased more than the inflation rates. Only medications with total annual payments >10 million USD/yr were included in the analysis to investigate financially meaningful price changes.

Results: Price increases were noted on average in 64% of already established medications (median 70%, range 45-74%), leading to an average additional extra cost of 242 million USD per year (range 140-330 million USD), for a total of 1.699 billion USD over the 7 years of observation. This extra cost represented 6.5-9% of the annual total Medicare Part B spending for antineoplastic medications.

Conclusion: The majority of already established injectable chemotherapeutics demonstrate price increases that lead to substantial additional financial cost to Medicare.
Poster: Does Household Size Predict Heart Failure Patients’ Adherence with Smartphone-Enabled Consumer-Grade Self-Monitoring Devices?

Presenter: Timothy Bober, Resident

Research Interest: Health Services
General Internal Medicine

Mentors: Bruce Rollman MD

Authors: Timothy Bober MD, Amy Anderson BS, Bruce Rollman MD

Introduction: Social support is an important predictor of recovery and survival in diverse patient populations, including those with cardiovascular disease. The mechanisms for this effect are multifactorial and may include adherence to clinician-recommended behavior changes. As part of a pilot study to develop a hybrid home- and center-based model of cardiac rehabilitation, we gave heart failure (HF) patients several consumer-grade home self-monitoring devices and then evaluated the relationship between their use of these devices and household size to inform development of our cardiac rehabilitation program.

Methods: We enrolled 30 patients with systolic HF (EF = 45%) and NYHA Class II-IV symptoms who owned a smartphone and consented to participate in our pilot following their 12-month final telephone assessment for a NIH-funded trial to treat depression. A study nurse made home visits to connect Bluetooth-enabled Nokia-brand scales, blood pressure cuffs, and smart watches to patients’ smartphones and then instructed them on how to use the devices. Afterwards, patients’ smartphones automatically transmitted use data to a password-protected Nokia website that abstracted and then linked to information we previously collected (e.g., sociodemographic and clinical characteristics including living arrangements).

Results: We enrolled 18 women and 12 men (23 white, 7 non-white; mean age: 65) into our pilot study. Their median household size was 2 (including the participant), and we classified them as either living in a “small household” (1-2 people; 20/30) or a “large household” (>2 people; 10/30). “Full adherence”, or use of all three devices, declined from 80% to 70% and 47% at 4-, 8-, and 12-weeks follow-up, respectively, while 17%, 30%, and 50% of patients used 1 or 2 devices (partial adherence) and 3%, 0% and 3% did not use any device at these time points. Rates of full- and partial adherence were similar by household size (e.g., full adherence 80%, 70%, 45% vs. 80%, 70%, 50% at weeks 4-, 8-, and 12, respectively.

Conclusion: HF patients’ adherence with home consumer-grade self-monitoring devices declines over time but remains high at the 12-week typical duration of a cardiac rehabilitation program, and household size did not affect patients’ adherence with these devices. We will present additional information on patients’ adherence with each individual device and other characteristics at the Conference.
**Poster Abstracts**

**55-R  Poster:** Deficits in Disease-Specific Knowledge in Individuals with Atrial Fibrillation

**Presenter:** Anna LaRosa, Resident

**Research Interest:** Health Services  
Cardiology

**Mentors:** Jared Magnani MD, MSc

**Funding Source:** NIH/NHLBI R56HL143010, Mobile Health Intervention

**Authors:** Anna LaRosa MD, Alexandra Pusateri BS, Andrew Althouse PhD, Utibe Essien MD, MPH, Jared Magnani MD, MSc

**Introduction:** Atrial fibrillation (AF) is a morbid, chronic condition. Patient success with AF requires understanding the disease, rationale for treatments, and the health literacy to participate in shared decision-making mandated by professional society guidelines. Social factors such as income and education influence health literacy and may influence disease knowledge. We assessed disease-specific knowledge in a cohort of patients with prevalent AF receiving medical treatment for the condition. We hypothesized that individuals currently receiving treatment would have good understanding of the condition, and that knowledge would be modified by education and income.

**Methods:** We enrolled a cohort of adults receiving care for non-valvular AF and prescribed oral anticoagulation at 4 ambulatory UPMC sites from 2016-18. Participants responded to 4 survey questions encompassing the ability to define AF; identify the indication for anticoagulation; define stroke; and estimate annual stroke risk. Responses were scored from 0-3 by 2 independent reviewers and adjudicated by a third. We collected patient demographics, clinical covariates, income and education with validated instruments. We used chi-square and ANOVA statistical tests to examine the association of education and income with responses to AF knowledge survey items in multivariable-adjusted models.

**Results:** Our cohort included 339 individuals (age 72.0±10.1; 42.5% women) with AF. The most frequent categories were $20-49,999 (29.2%) for income and high school or vocational training (34.5%) for education. Participants demonstrated moderate knowledge of AF (1.7±0.6; range 0-2), but had limited knowledge of the rationale for anticoagulation (1.3±0.7; 0-3) or stroke (1.5±0.8; 0-3). Patients with higher income did not have greater knowledge in AF (P=0.32 for trend), anticoagulation (P=0.27) or stroke (P=0.26). Individuals with bachelor or graduate degree had greater AF (1.8±0.5) and stroke (1.6±0.8) knowledge relative to those with high school or vocational training (1.4±0.7 and 1.2±0.9, respectively; P<0.001 for both estimates). Education was not associated with modification of knowledge regarding anticoagulation. Participants significantly overestimated their annual stroke risk with 50.4% of patients over-estimating risk by >20%; over-estimation of risk was inversely correlated with level of education but not reliably associated with income.

**Conclusion:** In a cohort of individuals receiving treatment for prevalent AF, we identified significant and fundamental gaps in patient knowledge about the condition. Improved understanding of this complex and chronic disease may enhance shared decision-making, engagement, adherence, and clinical outcomes. Interventions to improve patient understanding are essential, and our data indicate the relevance of systematic approaches not biased by presumption of health literacy due to patients' income or education.
**Poster: Elderly Patients’ and their Caregivers’ Perspectives on Medication Value: A Qualitative Study**

**Presenter:** Aimee Pickering, Resident

**Research Interest:** Health Services

General Internal Medicine

**Mentors:** Thomas Radomski MD, MS

**Funding Source:** KL2

**Authors:** Aimee Pickering MD, Megan Hamm PhD, Joseph Hanlon PharmD, MS, Carolyn Thorpe PhD, MPH, Walid Gellad MD, MPH, Thomas Radomski MD, MS

**Introduction:** Health systems are increasingly implementing deprescribing interventions to reduce elderly patients’ use of unnecessary or harmful medications. Shared decision making is essential to successful deprescribing, yet patients’ and caregivers’ perspectives on medication value and their willingness to stop a medication are poorly understood. Our objective was to identify the most significant factors that impact the perceived value of a medication from the perspective of patients and caregivers.

**Methods:** We conducted 6 focus groups (3 of patients; 3 of caregivers), each consisting of 6-8 community-dwelling adults aged ≥65 years, or their caregivers, who were prescribed ≥5 medications in 2018. We sampled participants with diverse sociodemographic backgrounds and varying forms of health insurance and explored their views on factors that enhance or diminish their perception of a medication’s value and motivate their decision to discontinue its use. Two members of the research team independently applied a codebook to transcripts of the focus groups, with discrepancies adjudicated by the principal investigator. We then conducted a thematic analysis to identify salient themes.

**Results:** We identified 3 key themes. First, participants cited effectiveness as the primary factor that caused them to consider a medication to be of high value and worth taking. Patients appraised effectiveness based upon perceived improvement in symptoms, such as pain, or objective improvement in clinical values, such as blood pressure. Caregivers considered these factors but also based their assessment upon a prescriber’s recommendation without directly observing clinical improvement. Second, patients and caregivers considered a medication to be of low value and not worth taking if it adversely affected their quality-of-life. Participants most frequently cited severity of side effects, discomfort associated with administration, or inconvenience in taking the medication. One caregiver noted, "if it's causing... debilitating pain or nausea... then I don't know if it is worth it... it's sacrificing your quality of life in your older years....” Third, while factoring less prominently, participants cited a medication’s cost as a consideration in determining its value, especially if it caused them to make material sacrifices.

**Conclusion:** We identified an interplay of factors, including perceived effectiveness, impact on quality of life, and cost as playing roles in patients’ and caregivers’ views of a medication’s value and their willingness to discontinue its use. Our findings will allow health systems to incorporate a patient-centered assessment of value into systems-based deprescribing interventions and enable prescribers to meaningfully engage older patients in shared decision making when deprescribing unnecessary or harmful medications.
**Poster Abstracts**

**57-R  Poster:** Is ICD 10 Better Than ICD 9 at Identifying Orbital Cellulitis

**Presenter:** Caroline Vloka, Resident

**Research Interest:** Health Services
  General Internal Medicine

**Mentors:** John Ng MD

**Authors:** Caroline Vloka MD, Alexander Vloka MD, John Ng MD

**Introduction:** The International Classification of Diseases (ICD) coding is primarily used for billing and research purposes. The ICD-10 was implemented in order to improve accuracy for coding of symptoms, diseases and procedures. The use of the ICD allows researchers to quickly identify charts with the diagnosis of interest in retrospective studies and reviews. The purpose of our study was to compare the accuracy of ICD-9 and 10 codes in the identification of orbital cellulitis (OC).

**Methods:** Charts of patients with ICD-9 (376.01) and ICD-10 (H05.011, H05.012 and H05.019) codes for OC from January 2010 to July 2017 were identified at a tertiary care center. The charts of the patients with ICD codes for OC were reviewed to confirm proper diagnosis by review of ophthalmology consult notes and positive CT/MRI imaging. Patients were not considered to have OC if there was no evidence of post-septal infection of the orbits on CT/MRI.

**Results:** Of the 152 patients identified by the ICD-9 and 10 codes for OC, 55 (36%) were pediatric (<18 years old), and 97 (64%) were adults. Forty-eight had no OC, instead were found to have an alternate diagnosis: pre-septal cellulitis (31), fungal infection (6), tumor or inflammatory process (8), orbital fracture (2) and one had no eye pathology. Twelve charts had no notes in the EMR and were not included in analysis. Radiographic confirmation of OC was found in 92 patients, 46 (54%) adults and 46 (84%) children. There was a significant difference in the accuracy of coding for OC in adults between ICD-9 and 10. OC was confirmed with imaging in 45% of adults identified with ICD-9 and 68% of adults identified with ICD-10 (p<0.05).

**Conclusion:** Our study validated the conversion to the ICD 10 coding system in identifying OC in adults. Both the ICD-9 and 10 were accurate in identifying the charts of children with OC, both having a positive predictive value (PPV) of 90%. However, there was significant improvement in the PPV of the ICD coding of adult patients with OC from 45% to 68% (p<0.05). This improvement is most likely due to the implementation of a specific code for pre-septal cellulitis in the ICD-10 (L03.213). Both the ICD-9 and 10 are more accurate at identifying patients with OC in the pediatric population compared to the adult population (p<0.05). This discrepancy is possibly due to the wider range of etiologies and presentations in adults.
**58-R Poster:** Morning Report for All: The Use of Podcasts for the Dissemination of Clinical Reasoning Tools

**Presenter:** Ryan Augustin, Resident

**Research Interest:** Medical Education
General Internal Medicine

**Mentors:** Sarah Tilstra MD

**Authors:** Ryan Augustin MD

**Introduction:** The use of social media and podcasts have drastically revolutionized medical education, resulting in a positive impact on learner engagement, collaboration, and professional development. However, the capability of these programs to disseminate high-quality and engaging resources for medical decision making has not been documented.

**Methods:** The podcast, Morning Report, is an audio podcast of a clinical reasoning session much akin to standard “morning report.” Two expert physicians discuss a complex case with sequential disclosure of clinical information. The recording is edited, uploaded to the website and iTunes, and distributed via Twitter. Focus is on the clinical reasoning process, concepts, and clinical pearls.

**Results:** Over 4700 episodes have been downloaded (Feb 2019). And although a majority of downloads occurred in OH & PA, listeners were documented worldwide (Fig. 1&2). A majority of episodes (61%) were downloaded via mobile applications, primarily the iTunes podcast app (Fig. 3). And in terms of listener retention, each episode is played for 77% of its total length, on average. Within the iTunes catalog, the podcast holds a 5-star rating, with 15 ratings to date. Most recently, learning objectives and questions have been posted on the website for each episode (via Google Forms) to aid in active listener engagement. Plans to collect qualitative data on the content, delivery, and usability of Morning Report are underway.

**Conclusion:** [1] Morning Report is an efficient, portable way to disseminate clinical reasoning concepts with the capability of reaching thousands of learners in a short amount of time, while allowing learners to critically assess, pause, and analyze the case along with the expert discussants. [2] The ability of the digital platform to track number of downloads, popularity of topics, and user comments is an advantage over typical educational delivery systems to guide content and delivery in real-time. [3] Disseminating clinical reasoning tools via podcasts is not only effective, but can also be done in a relatively inexpensive and efficient manner.
**Poster: Decreasing Barriers and Increasing Confidence: Ambulatory Advance Care Planning Internal Medicine Resident Curriculum**

**Presenter:** Adi Shafir, Resident

**Research Interest:** Medical Education
General Internal Medicine

**Mentors:** Julie Childers MD

**Authors:** Adi Shafir MD, Dio Kavalieratos PhD, Jane Schell MD, Julie Childers MD

**Introduction:** Patients are eager to participate in advance care planning (ACP) discussions, but there are numerous physician barriers to outpatient discussions. Education in overcoming these barriers are rare in residency programs.

**Methods:** Second and third year internal medicine residents participated in two 3-hour sessions during an ambulatory care rotation. The first session presented information about ACP; a conversation framework using the acronym REMAP (Raise the issue, respond to Emotion, Map patient values, Affirm the patient, and propose a Plan); drills practicing using REMAP, and documentation in the electronic medical record. Residents were asked to discuss ACP with a clinic patient in between sessions, and write down how the conversation went. During the second session, residents practiced ambulatory ACP skills using a simulated patient, and debriefed the homework. A pre-survey was completed by participants before the curriculum, and a post-survey was completed immediately after, ranking confidence and barriers on a 5-point Likert scale.

**Results:** 54 residents completed the pre-survey, and 50 completed the post-survey. Pre-post intervention medians were compared using Wilcoxon-Mann-Whitney U tests due to non-normal data. After completion of the curriculum, residents felt more confident bringing up ACP (p<0.001), discussing choosing a surrogate decision-maker (p<0.001), were more willing to bring up ACP (p=0.007), and felt it was more important to bring up ACP (p=0.002). Notably they no longer felt time was a barrier to discussing ACP (p<0.001), and no longer felt uncomfortable initiating the discussion (p=0.049).

**Conclusion:** An ambulatory ACP curriculum that includes a structured conversation framework and opportunities to practice with simulated patients is effective in improving resident confidence and willingness to complete ACP and help patients identify a surrogate decision maker. Future research will evaluate whether education leads to improvement in completion of AD.
60-R Poster: Implementation of an Online Case-based Clinical Reasoning Curriculum

Presenter: Benjamin Smith, Resident

Research Interest: Medical Education
General Internal Medicine

Mentors: Thomas Painter MD

Authors: Benjamin Smith MD, Michelle Fleshner MD, Josesph Rocco MD, Thomas Painter MD

Introduction: Clinical reasoning has the potential to reduce diagnostic error. Availability of standardized clinical reasoning education for learners is limited. We aimed to create a case-based clinical reasoning curriculum distributed online to promote learner engagement, and to determine the best means for curriculum distribution and whether there was a interest in this curriculum outside of our institution.

Methods: The curriculum was based on learning objectives chosen by the Clinical Reasoning Group, which are in line with those promoted by the Society to Improve Diagnosis in Medicine. The cases selected were felt to exemplify the potential for biases that could lead to diagnostic error. Each case was organized into sections separated by multiple-choice questions that prompted learners to analyze their clinical decision making and make work up decisions. The cases are inputted into the online survey platform Qualtrics and are distributed monthly via email to residents and faculty at UPMC and also via Twitter for open participation and discussion. Each case took 5-6 minutes to complete. Data collected includes number of persons completing each case and means of accessing the case.

Results: Three cases were distributed via email to Internal Medicine Residents and faculty at UPMC, and on Twitter by an educational account over three months. The number of participants for cases one, two, and three were 152, 183, and 246, respectively. The proportion of participants accessing the case from Twitter increased each month, initially with 30 participants from Twitter and later with 68 participants from Twitter. Participants indicated that they would appreciate more review of evidence-based testing, disease pathology, and mechanistic learning within the cases.

Conclusion: An online survey platform is an effective way to distribute clinical reasoning cases for educational purposes. The number of participants has steadily increased since initiation and feedback has overall been positive. In general, participants appreciate the accessibility of cases on smartphones, their brevity, and the interactive nature of the cases. Both email and social media have been effective platforms for distribution, but social media may have the ability to distribute educational materials more widely.
Poster: Evaluating the Role of a Formal CXR Curriculum on Housestaff Education

Presenter: Rachel Wojcik, Resident

Research Interest: Medical Education
General Internal Medicine

Mentors: Jared Chiarchiaro MD

Authors: Angela Suen MD, Rachel Wojcik MD, Michael Simonson MD, Nicholas Vu MD, Andrew Klobuka MD, Richard Zou MD, Jared Chiarchiaro MD

Introduction: Internal Medicine residents cite varying comfort levels with interpretation of chest radiographs (CXR) during clinical training. Being able to independently review CXRs is an important, but often overlooked, skill especially as formal interpretation may not be immediately available. The current gold standard for learning how to interpret CXRs at UPMC is through clinical rotations, MKSAP, and Radiology Rounds. To the best of our knowledge, a standardized educational imaging curriculum tailored to Internal Medicine residents does not exist. In conjunction with the Department of Radiology, we created a prospective case-based chest radiograph curriculum aimed to increase clinical competency and comfort with image interpretation.

Methods: Internal Medicine interns (n=75) at the University of Pittsburgh Medical Center were randomized in 1:1 fashion into control (n=37) and intervention arms (n=38). A pre-curriculum quiz and survey were administered to all interns during orientation, focusing on knowledge of and comfort in interpreting CXRs. Those randomized into the intervention arm were asked to voluntarily and anonymously participate. Each of the twelve cases included a brief patient case, de-identified CXR and a clinical-based multiple-choice question. Answers were accompanied by systematic image interpretation and case summaries. At the conclusion of the study, all interns will participate in a post-curriculum quiz and survey to reassess knowledge. Educational exemption was obtained by the local Institutional Review Board (PRO17070620).

Results: Seventy-two (96%) interns completed the pre-curriculum quiz with a mean score of 75%. Through the first 4 cases of the prospective curriculum, there is a 37% response rate among interns in the intervention arm, with a mean score of 63%. The most recent case received 5 responses of the 38 interns who received the email.

Conclusion: While there is demonstrated interest in the curriculum, we have encountered limitations in content delivery. As established in other small studies, we saw that the voluntary aspect of this intervention resulted in relatively few responses that continued to decrease over time. It seems that there are limitations in deploying a voluntary intervention via email, including internal motivation and email fatigue. Therefore, it may be difficult to assess for efficacy by the end of the 12-month study. However, it does glean information about the utility of email as a delivery platform in medical education.
62-R  **Poster**: HOPE for PACT: A Pilot Study of Organ Donor Registration Among Persons Living with HIV (PLWH)

**Presenter**: Divya Bhamidipati, Resident

**Research Interest**: Quality Improvement
General Internal Medicine

**Mentors**: Ghady Haidar MD

**Authors**: Divya Bhamidipati MD, Peter Veldkamp MD, Linda Despines, Colleen Sullivan, Susan Stuart, Deborah McMahon MD, Ghady Haidar MD

**Introduction**: Under the HIV Organ Policy Equity Act (HOPE Act), persons living with HIV (PLWH) may receive organ transplants from HIV-infected donors. However, awareness of the HOPE Act among PLWH remains low, as do rates of organ donor registration. Our study aimed at increasing the rates of organ registration and assessing attitudes toward organ donation among PLWH at UPMC’s HIV outpatient clinic (PACT).

**Methods**: This was a prospective, qualitative survey conducted from July through October 2018 among PLWH presenting for care at PACT. CORE, UPMC’s organ procurement organization, provided the organ donor registration cards. Staff gave patients CORE cards at check-in and asked patients to indicate if they were interested in learning more about organ donation (yes/no). Staff asked interested patients to complete the basic CORE registry card. The CORE cards included space that allowed patients to express their attitudes regarding organ donation. CORE staff uploaded information obtained via the completed CORE card into the national registry without any linkage to their HIV status. The institutional review board at the authors’ institution approved the study.

**Results**: Nine hundred ninety-one unique patients were seen at PACT for primary care visits during the study period, 760 of whom were provided with cards. Of these, 88% (670/760) returned the cards, of which 649 were fully completed. Nine percent (59/649) were already registered. Of the remaining 590 patients, 44% (259/590) expressed interest in donor registration, while 54% (321/590) did not. Of these 259 patients, one opted to defer registration and five did not fill out the form appropriately. Therefore, 43% (253/590) of patients completed the process required for organ donor registration. Among the 321 patients who declined to discuss organ donation, 63% (201/321) did not provide an explanation. Of those who provided an explanation, 19% (23/120) listed their HIV status as a reason not to register as an organ donor. Of these, 57% (13/23) cited HIV-infected status alone, whereas 43% (10/23) cited the presence of HIV and other comorbidities. Other reasons were lack of interest (48%, 40/120), the need for more time to consider organ donation (8%, 9/120), non-HIV comorbidities (3%, 3/120), religious beliefs (4%, 5/120), and distrust of the healthcare system (1%, 1/120).

**Conclusion**: Organ donor registration rates increased from baseline (9% to 43%), with minimal effort from the clinic staff and physicians. Integrating donor registration cards into HIV clinics is a feasible way of increasing awareness and donor registration rates among PLWH. Knowledge gaps among PLWH persist. HIV is still perceived as a contraindication for donation. Future efforts should focus on educating PLWH about the HOPE Act and on using the primary care setting to promote organ donor registration.
Introduction: Studies have shown that advance care planning (ACP) improves multiple outcomes, including higher satisfaction with healthcare, concordance between patient preferences and end-of-life care received, and reduction in hospitalizations (Houben 2014, Gade 2008). We believe that implementing a dedicated visit for ACP in patients who have been unable to accomplish it during regular office visits will ultimately improve patient satisfaction and longer term outcomes. This project aimed to evaluate how we are doing thus far in outpatient ACP, and look at one possible mechanism to increase the number of patients who complete it.

Methods: The population included patients randomly selected from a practice of five physicians at Senior Care, a geriatric primary care clinic associated with UPMC Shadyside Hospital. Baseline data was obtained prior to implementation of an Annual Wellness Visit (AWV) program, the goal of which was to schedule all patients with a CRNP to discuss multiple health-related issues, including ACP. Approximately eight months following AWV implementation, the same cohort of patients were reviewed. Chart review included baseline demographics, satisfaction of the Epic advance directive (AD) reminder, and documentation of any kind relating to ACP (this was based on a keyword search including “advance directive,” “living will,” “surrogate,” “POA,” or “power of attorney.”

Results: Charts of 50 patients were reviewed, 80% of these were female, with an even distribution among the 5 physicians of the practice. Patients aged from 67 to 98, with a mean of 82. Prior to implementing the AWV with a CRNP, only 39% of patients had an AD or other ACP document scanned into their charts; 18% had a documented ACP discussion of some type; 8% reported having an AD or living will at home; and 36% had no discussion or documentation. Unfortunately, eight months following implementation of the AWV, only two patients had attended an AWV, and only at one of these was ACP discussed.

Conclusion: This study highlights a major deficiency in ACP in the ambulatory setting. The addition of an AWV did not prove to be an effective means of increasing ACP, at least in this small cohort of geriatric patients over a short duration. The limited number of AWVs that were able to be scheduled likely also suggests a disinterest from the patient standpoint. Additionally the lack of a standardized practice of documenting ACP in Epic became evident in the data. More work is need in this area, including education for patients and physicians, along with better documentation strategies.
**Poster: Quality Assessment of "Life Sustaining Treatment" Documentation**

**Presenter:** Aaron Kuntz, Resident

**Research Interest:** Quality Improvement
General Internal Medicine

**Mentors:** Sandra Blakowski MD

**Authors:** Aaron Kuntz MD

**Introduction:** On January 11th, 2017, the United States Department of Veteran Affairs announced an initiative to improve personalization of care through advanced care planning. Veteran preferences for their health care are documented in the form of “Life Sustaining Treatment” notes (LST’s). These notes cover the issues of surrogacy, prognostic awareness, goals and values, and resuscitation preferences. The Pittsburgh VA implemented the LST note in mid-July of 2018, with August being the first full month of usage.

**Methods:** The objective of this quality assessment was to evaluate compliance with the mandated use of the “LST” note, as well as to investigate potential patient populations who would benefit from more focused advanced care planning discussions. A retrospective review of Emergency Department records from the Pittsburgh VA for the month of August was performed to assess frequency of LST completion and differences in LST trends and code statuses among various veteran subgroups. The first 300 veterans with Emergency Department records were analyzed. Age, gender, number of ED visits from August 2017 to August 2018, inclusive, and comorbidities were recorded, as well as the ultimate disposition for the patient. Data including completion and resuscitation preference was collected. Percentage completion and resuscitation preference will be compared across seven non-exclusive populations: above the age of 65, patients with greater than 4 ED visits in the last year, and patients with a diagnosis of any malignancy, any dementia, CHF, COPD, or a history of CVA.

**Results:** Overall, completion rate for the population of admitted patients was high, with over 90% of admitted patients having a documented LST. Patients with history of CHF, Cancer, Dementia and Stroke had over a 70% completion rate, with most patients being full code. 63% of patients with COPD had a completed LST. 50% of the geriatric population had a documented LST, and 64% were full code, percentages which did not appreciably increase with age. Few notes elaborated further on discussions or patient preferences, and some documentation was contradictory. Two thirds of LST’s were done during that patient’s most recent inpatient admission.

**Conclusion:** The results of this study identify several populations that would benefit from more intensive outpatient advanced care planning discussions, particularly patients with a high emergency department utilization rate, with COPD, and the very elderly (85+). The results also demonstrate education opportunities for providers regarding advanced care planning discussion, including common pitfalls.
**Poster: Interprofessional Management of Obstructive Lung Disease in an Urban Pennsylvania Free Clinic for the Uninsured**

**Presenter:** Christopher Marino, Resident

**Research Interest:** Quality Improvement
General Internal Medicine

**Mentors:** Faraaz Shah MD

**Authors:** Christopher Marino MD, Theo Pham PharmD, Sharon Connor PharmD, Mary Herbert MPH, Thuy Bui MD, Faraaz Shah MD

**Introduction:** Low-income and uninsured patients face numerous barriers to optimal management of obstructive lung disease and have a higher prevalence of asthma and chronic obstructive pulmonary disease (COPD). The Birmingham Free Clinic (BFC) aims to provide access to high-quality care and timely diagnosis for uninsured patients with obstructive lung disease in an interprofessional free clinic setting. Comprehensive pulmonary care at BFC includes a smoking cessation program, pharmacist-driven medication therapy management clinic, medication assistance programs, and a specialty pulmonary clinic with on-site spirometry offered every three months. This project identified patients with poorly-controlled obstructive lung disease and explored factors associated with disease control in order to optimize care.

**Methods:** A retrospective chart review was performed for all patients seen at the clinic with a diagnosis of asthma or COPD from January 2016 to June 2018. Cases were identified using ICD-10-CM diagnostic codes. A case report form was applied to abstract data on demographics, tobacco use, spirometry, medications, emergency department visits, and hospitalizations. Patients were classified as uncontrolled if chart review revealed: (1) daily albuterol inhaler use, (2) nighttime awakening, (3) functional limitations, or (4) emergency department visits or hospitalizations due to obstructive lung disease within the past year.

**Results:** A total of 106 adults (age 45 ± 15 years, 51% female) presented with obstructive lung disease over the 30-month period (asthma 75%, COPD 21%, combined asthma-COPD 4%). Seventy (66%) had no documented spirometry testing, demonstrating spirometry underutilization and reliance on clinical assessment for diagnosis. Forty-six (43%) reported ongoing tobacco use and nineteen (18%) reported former tobacco use. Twenty-nine (27%) had uncontrolled disease. Factors associated with poor control included active tobacco use (p=0.04), older age (p=0.03), male sex (p=0.01), and a diagnosis of COPD or combined COPD-asthma (p<0.01). Race and body mass index did not significantly differ between controlled and uncontrolled groups. Suboptimal control of obstructive lung disease resulted in 58 emergency department visits and 15 hospitalizations. A minority of patients (27%) continued to follow regularly at the clinic into 2018.

**Conclusion:** Management of obstructive lung disease in an uninsured population presents unique challenges as patients are at high risk of fragmented care and have limited access to diagnostic spirometry and appropriate therapy. This quality improvement study identified targets to optimize care in a free clinic setting including enhanced inter-visit follow up, pharmacist-assisted management, improved access to on-site spirometry, increased tobacco cessation efforts, and incorporation of validated assessment tools in asthma and COPD management.
Poster: Improving Anemia in Inflammatory Bowel Disease: Impact of the Anemia Care Pathway

Presenter: Thien-Bao Nguyen

Research Interest: Quality Improvement
Gastroenterology, Hepatology and Nutrition

Mentors: Jason Hou M.D., M.S., F.A.C.G.

Funding Source: VA HSR&D Center for Innovations (#CIN 13-413)

Authors: T. Peter Nguyen MD, Talha Qureshi MD, Ruifei Wang BS, Diana Willis, Rajesh Shah MD

Introduction: Anemia is a common complication of inflammatory bowel disease (IBD) associated with increased hospitalizations and reduced quality of life. Despite existing guidelines for anemia in IBD, it is frequently under-treated and the prevalence of anemia has remained high. To address this gap, the Crohn’s and Colitis Foundation developed the Anemia Care Pathway (ACP).

Methods: The ACP was implemented in one provider’s clinic from July 2016 through June 2017 and retrospectively studied. Run charts were used to identify shifts in iron deficiency screening and treatment as well as anemia prevalence. For supplementary analysis, results were compared to those of other providers in the same center who had been informed of the ACP and other anemia guidelines but were free to practice as desired.

Results: In the ACP-implementing clinic (n=213), anemias received iron therapy in only 30% of encounters at baseline but improved to 80% afterward. Concurrently, anemia prevalence decreased from 48% to 25%. Screening for iron deficiency, however, did not improve. In the clinics where the ACP was not implemented (n=427), there were no shifts in the prevalence of iron therapy nor the prevalence of anemia.

Conclusion: The baseline prevalence of anemia in IBD was high, yet rates of screening and treatment for it were low. Implementation of the ACP was not associated with improved screening rates, but it was associated with a 50% increase in iron therapy and a 24% decrease in the prevalence of anemia. Future refinements to the ACP should be focused on enhanced screening and follow up.
67-R  **Poster:** Inappropriate Aztreonam Usage Identified as an Opportunity to Reduce Pharmaceutical Expenditures

**Presenter:** Brandon Smith, Resident

**Research Interest:** Quality Improvement  
General Internal Medicine

**Mentors:** Mohamed Yassin MD

**Authors:** Brandon Smith MD, Joseph Tholany MD, Bridget Batykefer PharmD, Alaina Koval PharmD, Mohamed Yassin MD

**Introduction:** Targeting “low-hanging fruit” is a pillar of antimicrobial stewardship (AMS). Beta-lactam allergies (BLA) frequently restrict clinical decision-making and lead to utilization of alternative, less preferred antimicrobials making them an ideal AMS target. Prior studies have demonstrated that BLA are grossly over reported by patients. This study aimed to calculate the excess pharmaceutical expenditures incurred by utilization of aztreonam in patients who had previously (or subsequently) tolerated a beta lactam (BL).

**Methods:** Retrospective chart review was performed on inpatients >18 years old at our institution who received at least one dose of aztreonam during the 2017 calendar year. Data collected included: BLA, both prior and subsequent BL classes tolerated, number of doses and days of aztreonam administered. Patients were excluded from the analysis if they did not have a documented BLA or if they received aztreonam as targeted/de-escalation therapy. Cost of aztreonam therapy was then compared to the cost of alternative BL agents based on prior and subsequently tolerated classes of BLs. Comparator agents included: pipericillin/tazobactam (penicillin), cefepime (cephalosporin) and meropenem (carbapenem). Wholesale acquisition costs were used for each agent and comparator regimens were based on our health system-wide dosing guidelines adjusted for renal function.

**Results:** 132 patients met inclusion criteria. Of those patients, 88/132 (66.7%) had demonstrated tolerance of a BL agent. Specifically 69/132 (52.3%) previously and 19/132 (14.4%) subsequently tolerated a beta-lactam. Across the study, $40,768.84 was spent on aztreonam for patients with prior/subsequent BL tolerance. Cost for alternative therapy was estimated at $13,143.25 total; with an estimated cost difference of $27,625.59. Estimated cost difference for prior tolerance was $21,987.87 & subsequent tolerance $5,637.72.

**Conclusion:** Aztreonam is an uncommon but costly antimicrobial. This study demonstrated that reduction in aztreonam utilization based on prior tolerance of beta-lactam agents could lead to a meaningful reduction in pharmaceutical expenditures and serve as low-hanging fruit for an antimicrobial stewardship program.
Poster: Mitigation of Inappropriate Aztreonam Utilization by Preemptive Chart Review

Presenter: Brandon Smith, Resident

Research Interest: Quality Improvement
General Internal Medicine

Mentors: Mohamed Yassin MD

Authors: Brandon Smith MD, Bridget Batykefer PharmD, Alaina Koval PharmD, Mohamed Yassin MD

Introduction: In an ideal world, patients would receive the most efficacious & least toxic antimicrobial targeted for their specific infection. One frequently encountered limitation is a history of beta lactam allergy (BLA). According to the CDC 10% of US patients report a BLA, but studies have indicated less than 1% of the population is truly allergy. Due to these reported allergies, patients frequent receive alternative & less optimal therapy. Using aztreonam as a surrogate marker of BLA, this studied aimed at measuring the frequency of prior beta-lactam tolerance in patients with a reported BLA.

Methods: Retrospective chart review was performed on all inpatients >18 years old at our institution who received at least 1 dose of aztreonam during the 2017 calendar year. Data collected included: BLA, reaction type & date, current indication of aztreonam, & both prior and subsequent beta-lactam (BL) classes tolerated. Patients were excluded from the analysis if they did not have a documented BLA or if they received aztreonam as targeted/de-escalation therapy.

Results: 148 patients were reviewed. 137/148 had a documented allergy to at least 1 BL class. 178 total allergies were reported (patients with multiple allergies). PCN allergies were the most common 113/178. Hives/angioedema 64/178 were the most common reactions, followed by unknown 61/178 & rash 34/178. Three patients excluded for de-escalation. 65/134 patients had EMR documentation of tolerance of a BL agent: Cephalosporins were the most common, 39/65, followed by multiple classes 11/65, carbapenems 8/65, and PCN 7/65. Subsequently of those who had not previously tolerated a BL, 13/69 demonstrated tolerance of cephalosporins, 6/69 multiple classes, 5/69 carbapenems, 2/69 PCNs.

Conclusion: This study demonstrates that performing an EMR review of patients with BLA has the potential to identify a significant number of patients who have previously tolerated alternative beta-lactam agents thereby reducing use of less efficacious, more toxic alternative medications. 65/134 patients had demonstrated prior & 26/134 subsequently tolerated a BL. Most concerning is that only 3/91 patients tolerating a BL had an EMR reflective of that tolerance demonstrating a clear opportunity for future antimicrobial stewardship intervention.
69-R  Poster: Using Telemedicine to Overcome Barriers in Hypertension Management at Birmingham Free Clinic

Presenter: Rachel Wojcik, Resident

Research Interest: Quality Improvement
General Internal Medicine

Mentors: Thuy Bui MD

Authors: Rachel Wojcik MD, Thuy Bui MD, Mary Herbert MPH

Introduction: Hypertension disproportionately affects uninsured and underinsured patients in both the United States and globally, putting these patients at increased risk of heart attack and stroke. Patients at Birmingham Free Clinic face numerous barriers for their blood pressure management, such as irregular work hours, lack of transportation, finding childcare, or simply having poor insight into one’s own health conditions. Telemedicine is a growing aspect of medical care due to its lower cost, fewer resources, and patient convenience. To date, there are very few studies available evaluating efficacy in incorporating telehealth into a free clinic’s management of blood pressure.

Methods: This quality improvement project was designed to assess feasibility of a telemedicine blood pressure management intervention over a three-month time-frame. Ten to fifteen patients with uncontrolled hypertension and barriers to accessing clinic are being selected to participate on a rolling basis. All patients are given an automated blood pressure cuff, instructions on how to properly check blood pressure, and information about a low-salt diet. Their first month of medication is provided and a time is scheduled for follow-up via telephone, at which time changes in medication can be recommended based on their blood pressure recordings. Medication is prepared and dispensed by our pharmacy staff to a secure mailbox and patients are then followed-up in one to three weeks based on blood pressure readings. After three months, if their blood pressure is well-controlled, they may have a prescription sent to their pharmacy for a three-month supply.

Results: In the first month of the program, 5 patients have been enrolled and we are actively seeking to enroll approximately 5 to 10 more. We have successfully reached one patient with an initial blood pressure of 170/101 and after 3 weeks of daily medications, now has a blood pressure of 133/91 with only minor titration needed. Inability to reach patients via telephone is the main barrier encountered thus far.

Conclusion: This project has garnered significant interest from patients and we are hopeful that utilizing telemedicine for management of hypertension is feasible for a free clinic with limited resources. If successful, we will need to establish a more formal program, taking into account provider time outside of regular clinic hours and pharmacy’s capacity to mail medications.
70-R  **Poster:** Assessing the Adequacy on Hemodialysis in Inpatients with AKI

**Presenter:** Karim Yatim, Resident

**Research Interest:** Quality Improvement  
General Internal Medicine

**Mentors:** Paul Palevsky MD

**Authors:** Karim Yatim MD, Ranil DeSilva MD, Paul Palevsky MD

**Introduction:** Hemodialysis dose is routinely measured during outpatient ESRD HD sessions via urea kinetic models relying on pre-HD and post-HD BUN. Subsequently, dialysis parameters are adjusted accordingly to achieve an HD dose in compliance with published guidelines. This practice is not routine for inpatients with AKI, despite data suggesting differences in mortality at different delivered dialysis doses. The frequency of assessing dialysis dose for inpatients with AKI undergoing HD at our institution is unknown. Our QI study aims to measure the frequency of pre and post BUN measurement, as a surrogate for dialysis dose. Subsequently, we aim to reanalyze our data after an educational intervention to promote awareness amongst nephrology faculty and fellows. The overarching goal is to increase engagement in assessing HD adequacy amongst nephrologists.

**Methods:** To that effect, we conducted a retrospective EMR review of all HD sessions, administered to patients with AKI admitted to our facility over a two-month period (March-April 2017). The first six HD sessions per patient were analyzed.

**Results:** Pre-QI intervention, pre and post BUN were recorded in 2 of 38 patients (5.2%) and 2 of 199 HD sessions (1%) over 2 months. Currently, we are repeating our analysis for inpatients in the post-intervention period of Oct-Nov 2018.

**Conclusion:** Our data so far reveals that pre and post BUN are not routinely assessed for inpatients with AKI undergoing HD.
**Introduction:** Cystic fibrosis (CF), the most common lethal inherited condition among Caucasians in North America, is usually due to single amino acid mutations in the cystic fibrosis transmembrane regulator protein (CFTR). CF patients may have a variety of mutations between their two alleles, leading to a diversity of phenotypes within CF. Advances in the understanding of the mechanisms by which these mutations in CFTR cause clinical disease has informed the development of newly approved causal pharmacotherapy. One such mutation, G551D, which causes an isolated defect in transmembrane ion conduction, is highly amenable to potentiation by ivacaftor. DelF508, however, has a much less exuberant response, even with combination potentiator-corrector medications. While most current research is directed at duplicative potentiation and correction of mutant CFTR, it is important to recognize that endoplasmic reticulum-associated degradation (ERAD), first described at University of Pittsburgh, is in large part responsible for the decreased in vivo efficacy of correctors lumacaftor and tezacaftor. Given in vitro data that inhibition of the proximal steps of ERAD may be an effective method for increase membrane-based mature CFTR, particularly when combined with ivacaftor-lumacaftor, our group sought to use high-throughput testing to identify and then test inhibitors of the CHIP E3 ligase, a critical and relatively specific ubiquitinase, in the treatment of CF.

**Methods:** Using computer software (PocketQuery and FTMap), we identified three potential inhibitor pharmacophores. Commercially available compounds were screened using ZincPharmer, which yielded seven potential drugs; of these, compound 3.6 performed best in a simulated interaction with activated CHIP E3 ligase (LibDock).

**Results:** 3.6 was then shown to significantly decrease ubiquitination of immunopurified delF508 CFTR at physiologic concentrations. Additional, compound 3.6 increased CFTR expression in HEK cells transfected to expressed delF508 CFTR and works synergistically with lumacaftor to increase delF508 abundance and maturation.

**Conclusion:** Our data show that inhibition of proximal steps in ERAD shows promise as a novel pathway for the treatment of CF. Further, ERAD inhibition would overcome the primary mechanism of resistance by CF cells to the currently available therapies. Further studies are underway to optimize cell free and cellular assay systems, target other druggable sites of CHIP, improve compound efficacy, develop an SAR for the chemical series identified, and examine compounds in functional assays and in primary lung epithelial cells.
**72-R Poster**: Distinct Neuropsychological Phenotypes with Herpes Virus Shedding in HIV Infection

**Presenter**: Sunmin Park, Resident

**Research Interest**: Translational
Infectious Diseases

**Mentors**: Bernard Macatangay MD

**Authors**: Sunmin Park MD PhD, Omolara Fatukasi PhD, Yue Chen PhD, Arlene Bullotta BS, Sharon Riddler MD, Charles Rinaldo PhD, James Becker PhD, Bernard Macatangay MD

**Introduction**: HIV-associated neurocognitive disorder is prevalent among individuals virally suppressed on cART. We evaluated whether subclinical herpesvirus shedding in virally suppressed people with HIV (PWH) on ART correlates with neuropsychological phenotypes.

**Methods**: We assessed levels of EBV, CMV, and HHV-6 DNA in blood, throat washing, semen, urine, and stool at 4 timepoints over a 24-week period from 6 PWH and 7 age-matched seronegative men (median age, 43 yr) from the Multicenter AIDS Cohort Study. Shedding rate was the number of samples with (+) virus DNA/total number of specimens tested (max = 20 per virus). Participants with shedding rates that were higher than the median for their serostatus group were defined as high shedders. Domain T-scores were calculated based on the assessment of executive function, speed of information processing, attention and working memory, learning, memory, and motor with adjustment for age, education, ethnicity, and test frequency. Shedding rates for the 3 viruses were plotted against the mean T-scores for memory, learning, and speed of information (NP3T). Principal Component Analyses (PCA) and K-nearest neighbors algorithms were applied to transform the data for cluster analysis with each feature created by a weighted aggregate of all T-scores.

**Results**: PWH had median CD4+ T cell count of 854 and were virally suppressed for a median of 7 years. The total shedding rate for all 3 viruses combined was higher among PWH compared to controls (mean16 vs. 10.6, p=0.01; Mann-Whitney). PWH had more EBV shedding episodes detected (p=0.02, t-test) but no differences observed in CMV or HHV-6. Among PWH but not controls, the total herpesvirus shedding rate was negatively correlated with the NP3T score (r²=0.52 vs. r²=0.08; Fig 1). When the herpesviruses were analyzed separately, a meaningful association was only observed between EBV and NP3T. Distinct clusters of aggregate T-scores were observed by shedding rate and HIV serostatus. HIV positivity in both high and low shedders correlated with lower features compared to seronegative controls.

**Conclusion**: Distinct neuropsychological phenotypes can be identified by HIV serostatus and rate of shedding of EBV, CMV, and HHV-6, captured over a 24-week time course. PWH with higher subclinical shedding rates of EBV, CMV, and HHV-6 were associated with lower neuropsychological performance. Our study suggests there may be a potential link of persistent, subclinical herpesvirus infection to cognitive impairment in PWH.
**Poster: Novel Ticagrelor Coated Coronary Stent to Eliminate the Requirement for Dual Antiplatelet Therapy Post PCI**

**Presenter:** Jared Romeo, Resident

**Research Interest:** Translational General Internal Medicine

**Mentors:** John Pacella MD

**Funding Source:** Pennsylvania Department of Health CURE Grant

**Authors:** Jared Romeo DO, John Pacella MD, Ellen Gawalt PhD

**Introduction:** Percutaneous coronary intervention (PCI) for flow limiting coronary disease exceeds 1.8 million annually. Stent thrombosis (ST) is major mechanism of stent failure and its prevention requires the use of prolonged dual antiplatelet therapy (DAPT), risking bleeding. Additionally, 5% of PCI patients have atrial fibrillation, requiring triple oral anticoagulation therapy (TOAT), which further increases bleeding risk. Major bleeding rates range from 2.2% within 30 days and 12% in those requiring TOAT at 6 to 12 months. Post PCI bleeding is independently associated with increased mortality, yet an ideal system to minimize bleeding while preventing ST does not exist. Accordingly, we hypothesize that a novel ticagrelor coated stent (i.e. "TCS") utilizing a self-assembled monolayer (SAM) linker will preserve the local antiplatelet activity of ticagrelor to prevent ST, while minimizing systemic bleed associated with prolonged DAPT.

**Methods:** SAMs were formed on stainless steel coronary stents and used to immobilize ticagrelor via a Mitsonobu reaction. Linkage was characterized by diffuse reflectance infrared spectroscopy (DRIFT). The antiplatelet activity of the TCS was measured in vitro via adenosine diphosphate ELISA, flow cytometry for CD62P and CD41a, and scanning electron microscopy.

**Results:** Ticagrelor immobilization was characterized by DRIFT spectroscopy. Peaks indicative of the ticagrelor molecule include: hydroxyl groups at 3273 and 1324 cm⁻¹; aromatic peaks at 1608, 1518 and 1436 cm⁻¹, and an aryl ether at 1324 cm⁻¹. The peaks attributed to the self-assembled monolayer linker molecule include CH₂ peak at 2916 and 2850 cm⁻¹ and peaks in the spectrum attributed to P-O at 1119 and 995 indicating phosphonic acid bonding to the surface. Platelet activity via ELISA, mass spectroscopy, and a rat coronary model are ongoing.

**Conclusion:** We successfully created TCS stents with preservation of the ticagrelor structure. This novel stent design provides a potential alternative to DAPT as the tethered ticagrelor is active locally and on-site, eliminating the need for prolonged systemic DAPT and mitigating the associated bleeding complications. In vivo studies to assess the antiplatelet activity of the TCS are ongoing.
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1-A Poster: The IL-22/IL-22RA1 axis orchestrates innate immune responses against oropharyngeal candidiasis (OPC)

Presenter: Felix Aggor, Graduate Student

Research Interest: Bench (Basic Science) Rheumatology and Clinical Immunology

Mentors: Sarah Gaffen PhD

Funding Source: RO1 from NIH

Authors: Felix Aggor MSc, Timothy Break PhD, Bianca Coleman MS, Heather Conti PhD, Giraldina Trevejo-Nunez MD, Akash Verma PhD, Partha Biswas PhD, Scott Durum PhD, Jay Kolls MD, Mihalis Lionakis MD, Sarah Gaffen PhD

Introduction: Oropharyngeal candidiasis is an opportunistic infection of the oral mucosa predominantly caused by Candida albicans. While the protective role of IL-17 in OPC has been extensively studied, IL-22 remains largely unexplored. Here, we address the similarities and differences between IL-17 and IL-22 responses during OPC.

Methods: Il22 induction was assessed by qPCR and the cellular sources of IL-22 were determined by flowcytometry. RNASeq was performed to delineate Il22-dependent mechanisms. Localization of IL-22RA1 in murine tongue was assessed by immunohistochemistry and immunofluorescent staining was used to assess STAT3 activation during OPC.

Results: Like Il17a, Il22 is induced in murine tongue during OPC. Whereas IL-17a is mostly produced by innate CD4+TCRß+cells, IL-22 is dominantly produced by ?? T cells. Il22-/-mice are susceptible to OPC, although with lower fungal burdens compared to Il17ra/-/-mice. In contrast to Il17ra/-/-mice, Il22-/-mice had intact neutrophil recruitment to infected tongue. Neutralization of IL-22 in mice deficient in IL-17 signaling exacerbated OPC, suggesting some non-overlapping functions. RNASeq revealed subsets of genes that are Il17-dependent, Il22-dependent and dually-dependent. Genes such as Saa1/Saa2 and Il17 were only Il22-dependent and will be explored. We also assessed the role of IL-22RA1 and the IL-22-responsive cell types during OPC. As expected, Il22ra1/-/-mice are susceptible to OPC. Using radiation chimeras, we found that non-hematopoietic cells are the major responders to IL-22. IL-22RA1 is expressed in the suprabasal and basal oral epithelial layers only at the dorsal base of murine tongue. Surprisingly, this localization did not translate into significant differences in fungal burden between the front and back of the tongue. Deletion of IL-22RA1 in the suprabasal layer did not render mice susceptible to OPC. However, Il22ra1/-/-mice showed impaired STAT3 activation. Unexpectedly, deletion of STAT3 within suprabasal oral epithelial layer did not exacerbate OPC, perhaps suggesting a potential role in the basal layer.

Conclusion: Together, our results show that IL-22/IL-22RA1 acts non-redundantly with IL-17 to mediate protection against OPC. IL-22 targets a set of genes independently of IL-17 and the functions of these genes will be further explored to assess their mechanism of action.
**Introduction:** Relaxin has been considered as a potential therapy for patients with Idiopathic Pulmonary Fibrosis (IPF). We have previously shown, however, that a potential limitation to relaxin-based therapy for IPF is the loss of expression of the relaxin receptor Relaxin/Insulin Like Receptor 1 (RXFP1) in fibroblasts. The mechanism responsible for down-regulation of RXFP1 in IPF patients remains unclear.

**Methods:** Human lung fibroblasts established from donor and IPF lungs were cultured and used for expression analysis of both RXFP1 and miR-144-3p. TaqMan Advanced miRNA assay (hsa-miR-144-3p) was used in qPCR. Anti-miR-144-3p and miR-144-3p mimic were used to modulate endogenous miR-144-3p levels. RXFP1 protein expression was analyzed using Western blot. A lentiviral luciferase reporter containing the putative miR-144-3p binding sequence of human RXFP1 was created using pLenti-UTR-luc vector and tested for miR-144 function in Donor and IPF fibroblasts. Luciferase activity was measured by Promega Dual-luciferase assay system. Statistical analysis used t-test and ANOVA with significance assumed at p<0.05.

**Results:** To determine whether microRNAs play a role in RXFP1 gene expression, we employed a bioinformatics approach to identify microRNAs (miRs) that are predicted to target RXFP1 and identified a putative target site in the RXFP1 mRNA for miR-144-3p. In Situ Hybridization of IPF lung biopsies showed that miR-144-3p expression was present in fibroblastic foci. Further, we found that miR-144-3p was upregulated in IPF fibroblasts compared to donor lung fibroblasts. TGF increased the expression of miR-144-3p in both donor and IPF lung fibroblasts in a Smad2/3-dependent manner. AP-1 is required for constitutive expression of miR-144-3p. Forced expression of miR-144-3p mimic significantly reduced RXFP1 mRNA and protein levels and increased expression of the myofibroblast marker alpha-smooth muscle actin (alpha-SMA) in donor lung fibroblasts. IPF lung fibroblasts transfected with anti-miR-144-3p increased RXFP1 expression and reduced alpha-SMA expression. A lentiviral luciferase reporter carrying the WT 3’UTR of RXFP1 was significantly repressed in IPF lung fibroblasts whereas a reporter carrying a mutated miR-144-3p binding site exhibited less sensitivity toward endogenous miR-144-3p expression, suggesting that IPF lung fibroblasts have higher levels of miR-144-3p.

**Conclusion:** We identified a novel microRNA, miR-144-3p, that directly targets RXFP1 and acts as a negative regulator of RXFP1 mRNA and protein expression. TGFβ and AP-1 increased levels of miR-144-3p. Therefore, we speculate that miR-144-3p may play an important role in IPF. Rescuing RXFP1 expression using miR-144-3p antagonists could be a potential therapeutic strategy in lung fibrosis.
3-A  **Poster:** CD105 is a Mediator of Hematogenous Ovarian Cancer Metastasis

**Presenter:** Shoumei Bai, Junior Faculty

**Research Interest:** Bench (Basic Science)

**Research Interest:** Hematology/Oncology

**Mentors:** Ronald Buckanovich MD

**Funding Source:** R01

**Authors:** Shoumei Bai PhD, Wanhong Zhu BS, Lan Coffman MD, Esther Elishaev MD, Ronald Buckanovich MD

**Introduction:** Most high grade serous ovarian cancers (HGSC) initiate from the fallopian tube epithelium and then spread to the ovary. Genomic analyses suggest that, while rare HGSC may spread directly to the peritoneal cavity, most seed the ovary prior to abdominal dissemination. Similarly, animal models support a critical role for the ovary in driving intraperitoneal metastasis. Thus, HGSC cell recruitment to the ovary appears to be a critical component of HGSC cell metastasis.

**Methods:** We identified CD105 and other molecular markers expression using qRT-PCR, Western blotting, IHC and FACS analysis. shRNA knock-down and antibody blocking were applied to inhibit gene expression and protein activity, respectively. We further accessed CD105 function to promote tumor metastasis using in vitro migration, invasion assays, and in vivo metastasis tumor model systems.

**Results:** We identified CD105 (Endoglin, a TGF-β receptor family member) as a cell surface marker expressed on Serous Tubal Intraepithelial Carcinoma (STIC) cells, HGSC precursors in the fallopian tube epithelium, and on HGSC cells. High CD105 expression on tumor cells correlates with a metastatic signature. We show that hematogenous CD105(+) HGSC tumor cells home to the ovary and produce ascites/peritoneal spread. In contrast, while hematogenous CD105(-) cells can grow in the lung and liver, they do not spread to the ovary and subsequently do not spread to the peritoneal cavity. CD105 knockdown or blockade with a clinically relevant CD105 neutralizing mAb (TRC105), inhibit ovarian metastasis, reduce ascites, and impede growth of abdominal tumor nodules thereby improving overall survival in animal models of ovarian cancer.

**Conclusion:** Our data support CD105 as critical mediator of ovarian cancer spread to the ovary and implicate CD105 as a potential therapeutic target.
**4-A Poster: Platelets limit apoptotic lung epithelial cell death and protect mice against infection-induced lung injury**

**Presenter:** William Bain, Post-Doctoral Scholar

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Janet Lee MD

**Funding Source:** Individual NRSA (F32)

**Authors:** William Bain MD, Tolani Olonisakin BS, Minting Yu BS, Yanyan Qu PhD, Mei Hulver, Zeyu Xiong MD, MS, Huihua Li MD, Joseph Pilewski MD, Medhi Nouraie MD/PhD, Mallampalli Rama MD, Anuradha Ray PhD, Prabir Ray PhD, Robert Shanks PhD, Claudette St. Croix PhD, Janet Lee MD

**Introduction:** Thrombocytopenia is associated with worse outcomes in patients with the acute respiratory distress syndrome (ARDS), which is most commonly caused by infection and is marked by alveolar-capillary barrier disruption. However, the mechanisms by which platelets protect the host during infectious injury remain unclear. We hypothesize that platelets support alveolar-capillary barrier integrity after pathogen-mediated injury in part by limiting lung epithelial cell death.

**Methods:** Natively thrombocytopenic Mpl-/- mice, which are genetically deficient in the thrombopoietin receptor, were exposed to acute lung infection with the reference Pseudomonas aeruginosa (PA) strain PA14 and hypervirulent Klebsiella pneumoniae. Antibody-depletion of neutrophils in Mpl-/- mice was performed in select experiments. The cell-free supernatant of PA, PA14 ?xcpQ (a deletion mutant lacking the Type 2 secretion system outer membrane protein XcpQ), and PA14?exoTUY (a deletion mutant lacking the Type 3 secretion system exotoxins T, U, and Y) were administered to Mpl-/- mice. Platelet transfusion or administration of platelet releasates was performed in select experiments.

**Results:** Mpl-/- mice sustain severe lung injury and early mortality following acute intra-pulmonary Pseudomonas aeruginosa (PA) infection marked by alveolar barrier disruption and hemorrhagic pneumonia that is attenuated by platelet reconstitution. Klebsiella pneumoniae failed to induce hemorrhagic lung injury in Mpl-/- mice suggesting that alveolar injury was specific to PA. Although PA infection is associated with a brisk neutrophil response, depletion of neutrophil airspace influx failed to substantially mitigate PA-triggered alveolar barrier disruption in Mpl-/- mice. Rather, PA cell-free supernatant (SN) was sufficient to cause alveolar type II epithelial cell death in vivo and increased alveolar-capillary barrier disruption in Mpl-/- mice. Intra-tracheal administration of platelet releasate reduced PA SN triggered cell death as measured by PARP cleavage in lung tissue homogenates. Moreover, cell-free supernatant from PA with genetic deletion of the Type 2 secretion system but not the Type 3 secretion system mitigated lung injury in Mpl-/- mice, indicating a role for Type 2 secretion system products in PA induced lung injury.

**Conclusion:** These findings indicate that, while neutrophil airspace influx does not significantly contribute to infection-induced lung injury in the thrombocytopenic host, platelets protect against severe pulmonary complications from pathogen secreted virulence factors such as the PA Type 2 secretion system that promote lung injury and host cell death even in the absence of overt infection.
6-A Poster: Using Perturb-seq in primary human pulmonary fibroblast to better understand systemic sclerosis pathway pathologies

Presenter: Melissa Bulik, Graduate Student

Research Interest: Bench (Basic Science)
   Rheumatology and Clinical Immunology

Mentors: Robert Lafyatis MD

Funding Source: 5P50AR060780-07

Authors: Melissa Bulik MS, Eleanor Valenzi MD, Tracy Tabib MS, Christina Morse BS, John Sembrat MD, Mauricio Rojas PhD, Robert Lafyatis MD

Introduction: Systemic sclerosis (SSc) is a complex disease with both genetic and environmental factors affecting approximately 300,000 individuals in the United States. Presentation of symptoms vary greatly however tissue fibrosis, autoimmunity, and vasculature changes are defining characteristics of SSc. Disease progression and severity are variable with lung fibrosis leading to mortality in the most extreme cases. Previous work in our lab has identified differentially expressed genes within myofibroblast populations between normal and scleroderma lungs. Understanding molecular pathways involved in tissue pathology may lead to novel treatment plans which can be specific for subtypes of scleroderma patients. Perturb-seq, the combination of CRISPR-Cas9 gene editing and single-cell RNA sequencing (scRNA-seq) techniques, should allow for deeper understanding of the molecular mechanisms involved.

Methods: Primary human lung fibroblasts were isolated from normal lung explants. These cells were grown in culture with complete DMEM + 10%FBS. CRISPR-Cas9 Alt-R system was used to knockout FBXO32 and TCF12 in separate experiments. Following gene knockout, cells were grown for one week to allow for downstream effects, and then treated with TGFbeta or PBS as a control for 24 hours. Samples were antibody tagged with unique hashtags, pooled, and ran for scRNA-seq to study downstream effects of the gene knockout. Ingenuity Pathway Analysis (IPA) has been used to identify pathways involved.

Results: We are in the process of analyzing CRISPR-Cas9 knockouts, anticipating that targeted gene deletion will occur in some of the cells within each sample. Using scRNA-seq and bioinformatics software, we will separate the cell types based on transcriptomic profiles. We anticipate identifying downstream gene regulation in both Transcription Factor 12 (TCF12) and F-Box Protein 32 (FBXO32).

Conclusion: Perturb-seq can aid in delineating important pathways in SSc pathology. IPA will aid in the process of recognizing downstream effects caused by gene alteration. Continued analysis of the data is necessary to identify additional genes and pathways of interest.
Poster: Comprehensive Mapping of Immune-Epithelial Interactions in Severe Asthma Using Machine Learning Analysis of Multi-omics Data

Presenter: Matthew Camiolo, Post-Doctoral Scholar

Research Interest: Bench (Basic Science)

Pulmonary, Allergy and Critical Care Medicine

Mentors: Anuradha Ray PhD

Funding Source: T32

Authors: Matthew Camiolo MD, Xiaoying Zhou PhD, Timothy Oriss PhD, Wei Chen PhD, Jay Kolls MD, Kari Nadeau MD, Sally Wenzel MD, Anuradha Ray PhD

Introduction: Asthma is a common disease, affecting more than 300 million people worldwide. Though well controlled in most, a subset of patients experience refractory symptoms, accounting for nearly half the health care expenditure on asthma in the US. Time of flight mass cytometry (CyTOF) offers an opportunity to characterize the inflammatory milieu present in bronchoalveolar lavage (BAL) in unprecedented detail. Pairing this technology with gene expression data from lung epithelial and immune compartments yields the most comprehensive understanding of SA to date.

Methods: Healthy controls (HC) as well as patients with mild to moderate (MMA) and severe asthma (SA) as defined by ERS/ATS guidelines underwent bronchoscopy. BAL cells were stained with heavy metal conjugated antibodies followed by acquisition on the Helios CyTOF instrument and downstream analysis using Phenograph. Bronchial epithelium and BAL cell compartments were harvested and RNA was isolated and subjected to sequencing. After library preparation and count normalization, bronchial epithelial cell (BEC) samples were clustered together using the most variant transcripts in the data set. Differential expression analysis of BAL samples was based on BEC clustering.

Results: High dimensional flow cytometry of BAL from 7 HC, 15 MMA and 19 SA patients revealed 31 cells clusters based on staining of 33 surface markers. Network construction for covariant cell types demonstrates neighborhoods that vary together within the data set. Patient level grouping reveals 4 clusters defined by distinct cell populations. One SA-enriched patient cluster demonstrates high levels of IFN-? production driven by greater numbers of T-cells. The other patient clusters are defined by innate immune lineages including basophil/mast cells and macrophages that vary in relative abundance and Type 2 cytokine elaboration. Gene expression analysis of BEC reveals 3 patient clusters, two of which enriched for SA cases. One SA cluster demonstrates high levels of Type 2 inflammation and strong relationship with mast cell/basophils in BAL. Another showed low levels of Type 2 inflammation despite housing a third of patients with clinically severe disease. GSEA of this cluster identifies interferon and IL-6 pathway activation, suggesting Type 1 polarized immune response. These data were corroborated with expression data from BAL cells, underscoring networks of interacting cytokines between cellular compartments.

Conclusion: Comprehensive immunophenotyping of BAL samples identifies stereotyped derangements associated with cytokine signatures and reciprocal epithelial response within severe asthma. Correlative mapping of receptor-cytokine pairings across BEC and BAL offers insight into pathways driving inflammation may guide future targeted interventions.
Introduction: Focal segmental glomerulosclerosis (FSGS) and other proteinuric glomerulonephritides are major causes of progressive chronic kidney disease (CKD). Treatment options for these diseases are limited. Histone deacetylase inhibitors (HDACis) increase lysine acetylation in nucleosomal histones, allowing for increased transcriptional activity. The 4-phenylthiobutanoic acid (PTBA) analogue UPHD186 is an HDACi that has been shown to accelerate renal recovery and reduce fibrosis after ischemia-reperfusion injury or unilateral ureteric obstruction in mice. However, UPHD186 has not been tested in proteinuric CKD. We hypothesized that UPHD186 administration after glomerular injury would attenuate proteinuria and glomerular injury in response to an experimental FSGS model caused by adriamycin (doxorubicin).

Methods: To explore our hypothesis, we subjected 18 BALB/c mice to Adriamycin (8 mg/kg IV). On day 7, surviving mice were stratified according to proteinuria and randomized to receive either UPHD186 or vehicle. All mice received intraperitoneal injections of UPHD186 or vehicle at 50mg/kg on day 9 through day 15 post-adriamycin. Proteinuria was evaluated using enzyme-linked immunosorbent assay on days 7, 16, 23 and 28 post-adriamycin. Concurrent creatinine assays were performed to normalize proteinuria to urinary creatinine excretion (urine protein-to-creatinine ratio).

Results: Of the 18 mice that received Adriamycin, 5 died prior to completing the 7 day course of IP injections. 1 mouse was excluded because of extremely low proteinuria and high urine creatinine value, suggesting lack of glomerular injury. Overall, 6 mice in the vehicle group and 4 in the HDACi group survived to the final day 28 ELISA. Although there was no statistically significant difference in proteinuria between groups receiving HDACi versus vehicle, there was a trend towards proteinuria reduction in all mice in the HDAC group. Furthermore, the 2 mice with highest increases in proteinuria were in the vehicle group.

Conclusion: UPHD186 administration after glomerular injury by adriamycin demonstrated a trend towards proteinuria reduction when compared to vehicle. However, this difference was not significant and our study suffered from a high rate of attrition. It is unknown whether the 2 mice in the vehicle group with very high levels of proteinuria represent outliers versus a typical response to the Adriamycin FSGS model. Future experiments should involve a larger sample size, and may benefit from pump implantation for drug delivery to reduce injection burden. In conclusion, our data suggest that UPHD186 may attenuate proteinuria in mice subjected to glomerular injury, although more studies are needed to confirm this.
9-A Poster: Frataxin deficiency induces endothelial replication stress, DNA damage response, and senescence to promote pulmonary hypertension

Presenter: Miranda Culley, Medical Student

Research Interest: Bench (Basic Science)  
VMI

Mentors: Stephen Chan MD, PhD

Funding Source: Individual NRSA (F32)

Authors: Miranda Culley BA, Jingsi Zhao MS, Ying Tang MS, Vinny Negi PhD, Yi Yin Tai MS, Dror Perk Undergraduate student, Qijun Yu MD, PhD, Thomas Bertero PhD, Adam Handen MS, Seungchan Kim PhD, Gil Speyer PhD, Mingxia Gu PhD, Marlene Rabinovitch PhD, Stephen Chan MD, PhD

Introduction: Endothelial iron-sulfur (Fe-S) cluster deficiency promotes pulmonary hypertension (PH), but the pathogenic mechanisms are incompletely defined. Frataxin (FXN) controls Fe-S cluster assembly and mitochondrial respiration; however, less is known about FXN-dependent DNA replication and integrity. FXN mutations cause Friedreich’s ataxia (FRDA) and hypertrophic cardiomyopathy, often accompanied by PH. We hypothesized that FXN deficiency, due to genetic or acquired triggers, disrupts endothelial Fe-S-dependent DNA replication to promote PH.

Methods: Human pulmonary arterial endothelial cells (PAECs) and induced pluripotent stem cell-derived endothelial cells (iPS-ECs) from FRDA patients were studied. RNA sequencing was performed along with gene set enrichment analysis (GSEA). Endothelial-specific FXN knockout mice and mice with FXN RNAi delivered to the endothelium were studied.

Results: In PAECs, hypoxia (0.48-fold change ± 0.05, P<0.01, mean ± SEM) and IL-1 (0.47-fold change ± 0.01, P<0.05) decreased FXN. Inhibition of the epigenetic modulators BRD2/4 rescued expression. Acute FXN knockdown by RNAi decreased Fe-S clusters (0.57-fold change ± 0.05, P<0.01), increased BrdU incorporation (2.49-fold change ± 0.07, P<0.01) and the percentage of PAECs in S-phase but not cell number, signifying S-phase arrest. Double-stranded DNA breaks increased, reflected by induction of the DNA damage response (DDR) factor phosphorylated gamma-H2AX. RNA sequencing and GSEA in FXN-deficient PAECs revealed 203 pathways related to DNA replication and damage (FDR<0.05). PAECs with chronic FXN deficiency exhibited persistent DDR and cell cycle arrest. Moreover, FRDA iPS-ECs revealed elevated DDR and senescence markers, p16 and p21. Pharmacologic (RVSP 34.31 mmHg ± 0.18 v 29.77 ± 0.93, P<0.05) and genetic endothelial FXN deficiency in hypoxic mice promoted PH.

Conclusion: Genetic or epigenetic endothelial FXN deficiency impairs Fe-S-mediated DNA synthesis leading to DNA damage and senescence, thus promoting PH. Our results emphasize FXN-specific endothelial replication stress as a novel pathobiologic phenotype in this disease, thus endorsing therapies that relieve genotoxic processes and senescence in PH.
11-A  Poster: Effects of Stretch on the Bladder Umbrella Cell Apical Junctional Complex

Presenter: Amity Eaton, Graduate Student

Research Interest: Bench (Basic Science)  
Renal-Electrolyte

Mentors: Gerard Apodaca PhD

Funding Source: Individual NRSA (F31)

Authors: Amity Eaton BS, Dennis Clayton BS, Wily Ruiz BS, Marcelo Carattino PhD, Gerard Apodaca PhD

Introduction: The urothelium must maintain its integrity as the bladder fills and voids. A critical component of the epithelial barrier is the apical junctional complex (AJC), which circumscribes polarized epithelial cells at their apical pole. The AJC includes the apical tight junction (TJ), subjacent adherens junction (AJ), and associated junctional actin ring. We previously reported that the TJ ring of the umbrella cell layer of the urothelium expands during bladder filling and contracts with voiding. However, it remains unknown whether the AJ is similarly affected, and the identity of the underlying machinery that drives these changes.

Methods: To assess changes in the umbrella cell AJC during the bladder cycle we examined three groups of rat bladders: 1) full bladders filled for 2.5 hours; 2) voided bladders filled for 2.5 hours and voided for five minutes; and 3) quiescent bladders which were never allowed to fill.

Results: We observed the following: (1) Like the TJ ring, the AJ ring expanded during filling and contracted with voiding. (2) In addition to actin, which was concentrated in a ring interposed between the TJ and AJ, alpha-actinin was associated with the AJC ring, as was non-muscle myosin IIA. (3) The actin disrupting agent cytochalasin D, as well as inhibitors of formins (SMIFH2) or Arp2/3 (CK869), decreased expansion of the AJC ring. Surprisingly, treatment with blebbistatin, an inhibitor of myosin II-dependent contraction, had no effect on the expansion of the AJC ring. (4) An inhibitor of exocytosis (brefeldin-A), demonstrated a strong inhibitory effect on AJC ring expansion. (5) To specifically target the exocytic machinery we expressed dominant-negative (DN) mutants of Rab8a, Rab11a, or Rab13. Whereas DN-Rab13 significantly decreased expansion of the AJC ring during bladder filling, DN-Rab8a and DN-Rab11a, did not. (6) Unlike expansion of the AJC ring, its voiding-induced contraction was strongly inhibited by blebbistatin and was also significantly inhibited by cytochalasin D. (7) Intriguingly, AJC ring contraction was also inhibited by the endocytosis inhibitor Pitstop2 or expression of DN-Dynamin2. Moreover, DN-RhoA similarly impaired AJC ring contraction.

Conclusion: Our studies suggest that an important mechanism by which the urothelium retains continuity in the face of cyclical changes in volume is expansion and contraction of the AJC ring. Whereas ring expansion depends on actin polymerization, it also requires exocytosis, presumably of vesicles containing AJC-associated membrane proteins. In contrast, contraction of the AJC ring is likely driven by actomyosin contraction of the AJC ring and endocytosis of excess AJC proteins.
**Poster Abstracts**

**12-A Poster:** Interleukin-6 mediates mobilization of neutrophils from the bone marrow in pulmonary hypertension

**Presenter:** Jonathan Florentin, Post-Doctoral Scholar

**Research Interest:** Bench (Basic Science)

VMI

**Mentors:** Partha Dutta PhD

**Funding Source:** T32

**Authors:** Jonathan Florentin PhD, Jingsi Zhao BSc, Yi-Yin Tai BSc, Stephen Chan PhD, Partha Dutta PhD

**Introduction:** Myeloid cells, such as neutrophils, are important in disease pathogenesis. Neutrophils are produced in the bone marrow in high quantity in vascular diseases like pulmonary hypertension (PH). Egress of newly generated neutrophils from the bone marrow into the blood is the first step towards the recruitment of these myeloid cells into the lungs, resulting in inflammation and organ remodeling. However, the mechanisms of neutrophil egress from the bone marrow in disease conditions are poorly understood.

**Methods:** Using computational flow cytometry, we observed increased number of neutrophils in the lungs of patients and mice with PH. Additionally, RNA sequencing on total lung tissue of mice with PH revealed that IL-6 pathway was one of the most significantly upregulated pathways, indicating the role of IL-6 in PH pathogenesis.

**Results:** In line with this observation, the blood of patients and mice with PH contained elevated levels of IL-6. Transgenic mice overexpressing IL-6 in the lungs had increased neutrophil egress from the bone marrow, resulting in exaggerated neutrophil recruitment into the lungs, and exacerbated lung remodeling and right ventricular systolic pressure (RVSP). We observed that IL-6-triggered neutrophil egress from the bone marrow was dependent on IRF-4-mediated CX3CR1 expression. Genetic deficiency of Cx3cr1 in hematopoietic cells in mice overexpressing IL-6 in the lungs significantly reduced the egress of neutrophils from the bone marrow, resulting in fewer neutrophils in the lungs, and ameliorated pulmonary remodeling and RVSP.

**Conclusion:** Altogether, these data demonstrate a novel mechanism of neutrophil egress from the bone marrow and reveal new therapeutic target to curtail neutrophil-mediated inflammation in disease conditions.
**Poster Abstracts**

**13-A Poster:** Pharmacological Inhibition of FoxO Transcription Factors Reduces NO Signaling Through Downregulation of sGC

**Presenter:** Joseph Galley, Graduate Student

**Research Interest:** Bench (Basic Science)

VMI

**Mentors:** Adam Straub PhD

**Funding Source:** Louis J. Ignarro Cardiovascular Fellowship

**Authors:** Joseph Galley BA, Biochemistry, Megan Miller BS, Scott Hahn MSc, Brittany Durgin PhD, Adam Straub PhD

**Introduction:** Nitric oxide (NO) stimulates soluble guanylyl cyclase (sGC) activity leading to elevated intracellular cyclic guanosine 3', 5'-monophosphate (cGMP) and subsequent vascular smooth muscle relaxation. It is known that downregulation of sGC expression attenuates vascular dilation and contributes to the pathogenesis of cardiovascular disease. However, it is not well understood how sGC transcription is regulated.

**Methods:** Cultured rat aortic smooth muscle cells (RASMC) and isolated mouse thoracic aortas were treated with the small molecule inhibitor, AS1842856, in order to inhibit FoxO transcription factor activity. Endpoint measurements in cultured RASMC involved western blot analysis of protein, RT-qPCR of RNA, and enzyme-linked immunosorbent assay (ELISA) of cGMP produced. In isolated mouse aorta endpoint measurements were determined by immunohistochemistry staining for protein and NO-dependent vasodilation myography measurements.

**Results:** AS1842856 significantly blunts sGC a and β mRNA expression by more than 90%. These effects are dose-dependent and concomitant with greater than 90% reduced expression of the known FoxO transcriptional targets, glucose-6-phosphatase (G6Pase) and growth arrest and DNA damage protein 45 a (Gadd45a). Similarly, sGC β protein expression showed a dose-dependent downregulation. Consistent with the loss of sGC mRNA and protein expression, pre-treatment of RASMC with AS1842856 decreased sGC activity measured by cGMP production following stimulation with an NO donor. Isolated aortas have significantly blunted sodium nitroprusside (SNP)-induced (NO-dependent) vasorelaxation and a 42% decrease in sGC expression after 48-hour FoxO inhibitor treatment.

**Conclusion:** Taken together, these data are the first to identify that FoxO transcription factor activity is necessary for sGC expression and NO-dependent relaxation.
14-A Poster: New Insights into Endothelial-To-Mesenchymal Transition in Pulmonary Hypertension: Potential Role for Ezrin-radixin-moesin-binding phosphoprotein 50

Presenter: Anastasia Gorelova, Graduate Student

Research Interest: Bench (Basic Science)
VMI

Mentors: Imad Al Ghouleh PhD

Funding Source: Cotswold Foundation Fellowship

Authors: Anastasia Gorelova MSc, Vinny Negi PhD, Anas Alsuraimi, Ying Tang, Stephen Chan MD, PhD, Imad Al Ghouleh PhD

Introduction: Pulmonary arterial hypertension (PAH) is a cardiovascular disease defined by increased blood pressure in the lung circulation. The disease manifests in extensive vascular remodeling propagated, in part, by dysregulated production of vasoactive compounds and inflammatory molecules by the activated endothelium. Recently, endothelial-to-mesenchymal transition (EndoMT), a cellular process that primes endothelial cells to lose their surface markers (e.g. PECAM and VE-cadherin) and acquire smooth muscle cell-like phenotype and markers, was reported to contribute to PAH-associated EC dysregulation. In the current study, we investigated molecular mechanisms upstream of EndoMT activation under PH-related conditions. Despite some evidence of a role for Ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50) in the systemic circulation, its role in PAH or the pulmonary vasculature has not yet been defined. We therefore hypothesized that PAH induces interruption of EBP50 in the vascular endothelium, leading to EndoMT.

Methods: Human pulmonary artery endothelial cells (HPAECs) were used for in vitro studies. For in vivo PAH, Sprague-Dawley male rats were injected with monocrotaline (60mg/kg, 3wk).

Results: EBP50 expression was decreased in lung tissue from monocrotaline-treated rats. In vitro, treatment of HPAECs with PAH-related cytokine interleukin 1 beta (IL1b) reduced EBP50 expression, and increased expression (mRNA: 2.77±0.12-fold from vehicle, n=3, p<0.0001) and nuclear abundance of EndoMT-associated transcriptional repressor Snail. IL1b-induced upregulation of Snail was correlated with a decrease in endothelial markers PECAM and VE-cadherin, indicating an early stage of EndoMT progression. EBP50 gene knockdown in unstimulated HPAECs resulted in an increase in Snail expression (mRNA: 1.53±0.16-fold from scrambled siRNA, n=3, p<0.05) and a trend towards increased nuclear abundance of Snail protein, indicating a potential causal link between EBP50 and EndoMT.

Conclusion: Our findings demonstrate a new role for EBP50 in PAH and support that dysregulation of this protein can drive manifestations of EndoMT via upregulation of Snail, thus opening doors for development of novel therapeutic approaches targeting EBP50 in PAH.
**Poster Abstracts**

**15-A Poster:** A protective role for NCOA7 deficiency in the development of pulmonary arterial hypertension

**Presenter:** Lloyd Harvey, Medical Student

**Research Interest:** Bench (Basic Science)
Cardiology

**Mentors:** Stephen Chan MD, PhD

**Funding Source:** Individual NRSA (F32)

**Authors:** Lloyd Harvey BS, Wei Sun MD, PhD, Vinny Negi PhD, Adam Handen MS, Jingsi Zhao MS, Yi-Yin Tai MS, Miranda Culley BA, Ying Tang MS, Raymond Benza MD, Zandrea Ambrose PhD, Stephen Chan MD, PhD

**Introduction:** There is an increasing appreciation of how the immune system and its dysregulation are emerging drivers of pulmonary arterial hypertension (PAH). Previous literature has shown that inflammatory processes are inextricably linked to pulmonary vascular remodeling with reports of elevated cytokines in PAH patients. Accordingly, our group took interest in nuclear receptor co-activator 7 (NCOA7), where sparse literature has implicated NCOA7 as having an important role in innate immunity. As such, the aberrant behavior of pathogenic endothelial cells (ECs)—as conditional innate immune cells—may perhaps be governed by NCOA7. In line with this notion, our preliminary data have shown that a truncated form of NCOA7—isoform 4—is preferentially upregulated under known triggers of PAH, implicating it as a strong candidate in understanding EC dysfunction. We hypothesize that acquired (ie, HIV), environmental, and genetic stimuli induce expression of NCOA7 isoform 4, resulting in EC dysfunction and the pathogenesis of PAH.

**Methods:** Human pulmonary arterial endothelial cells (PAECs) were studied for in vitro assays. PAECs were also co-cultured with human CD4+ T cells in the absence or presence of HIV.

**Results:** We have demonstrated dramatic upregulation of NCOA7 in PAECs under a myriad of proinflammatory (eg, IL-1ß & HIV) and genetic (eg, ACRVL1, BMPR2, EIF2AK4, & ENG) triggers of PAH. Moreover, siRNA knockdown of NCOA7 abrogated apoptosis and significantly enhanced the angiogenic capacity of PAECs, indicating its significance in underlying EC biology. Examining regulatory elements, a transcription factor binding site (TFBS) for STAT1 was found to contain potentially disease-relevant SNPs and subsequent RNAi of STAT1 under IL-1ß was found to significantly attenuate NCOA7 expression. Accordingly, an electrophoretic mobility shift assay was performed to reveal differential protein binding at a SNP located within the TFBS, suggesting that the SNP may perhaps be controlling STAT1 binding and thus NCOA7 expression.

**Conclusion:** Loss of NCOA7 abrogates apoptosis and enhances angiogenesis, thereby serving as a protective mechanism against EC dysfunction and PAH. In addition, our data suggest a potential functional relevance for the SNP in controlling NCOA7 expression, perhaps via STAT1 binding.
Introduction: OXA-232 is a class D β-lactamase that hydrolyzes penicillins at a high level but hydrolyzes expanded-spectrum cephalosporins and carbapenems at a low level. For this reason, clinical strains producing OXA-232 enzymes are sometimes susceptible or intermediate to carbapenems, making it difficult to identify them in clinical microbiology. We describe the rapid development of carbapenem resistance in sequential clinical isolates of Raoultella ornithinolytica carrying blaOXA-232 in part due to the acquisition of OmpC and OmpF porin mutations.

Methods: MICs were determined by the broth microdilution method. Carbapenemase production was confirmed by the modified carbapenem inactivation method. Whole genome sequencing (WGS) was conducted for strain comparison and genome-wide variant discovery. In order to define the contributions of these variants to carbapenem resistance, the subsequent carbapenem resistant isolates were complemented with the ompC and ompF genes from the initial carbapenem susceptible R. ornithinolytica isolate.

Results: WGS analysis identified non-synonymous mutations in ompC and ompF in carbapenem-resistant isolates that were not present in the initial carbapenem-susceptible isolate. Complementation of the carbapenem resistant isolate with the wildtype ompC gene decreased the ertapenem MIC from 512 mg/L to 256 mg/L and the meropenem MIC from 32 mg/L to 16 mg/L. Complementation of the ompF gene decreased the ertapenem MIC from 512 mg/L to 16 mg/L and the meropenem MIC from 32 mg/L to 2 mg/L. Complementation of both ompC and ompF did not lead to an additional reduction of MIC beyond that provided by ompF alone.

Conclusion: Rapid development of carbapenem resistance in blaOXA-232 - carrying R. ornithinolytica was associated primarily with defective OmpF.
17-A Poster: Mitochondrial Adenine Nucleotide Translocase influences ciliary function and airway homeostasis

Presenter: Corrine Kliment, Junior Faculty

Research Interest: Bench (Basic Science)
   Pulmonary, Allergy and Critical Care Medicine

Mentors: Steven Shapiro MD

Funding Source: K08

Authors: Steven Claypool PhD, Josiah Radder MD, PhD, Frank Sciurba MD, Yingze Zange PhD, Alyssa Gregory PhD, Jennifer Nguyen BS, Ramana Sidhaye MD, Steven Shapiro MD, Douglas Robinson PhD

Introduction: Airway hydration and ciliary function are biological processes that are critical to airway homeostasis and are dysregulated in several diseases, notably chronic bronchitis and chronic obstructive lung disease (COPD). COPD is the 4th leading cause of death in the US and is impacted by cigarette smoking with no therapeutic options that reverse pathogenesis or mortality.

Methods: To identify new relevant pathways, we utilized the amoeba Dictyostelium discoideum as a novel comparative discovery tool for lung biology. We identified a gene that was protective against cigarette smoke induced cell death. We then evaluated the role in human bronchial epithelial cells and human lung disease, namely COPD.

Results: We identified adenine nucleotide translocase (ANT), a canonical mitochondrial ADP/ATP transporter, as being protective against cigarette smoke in Dictyostelium and human bronchial epithelial cells. In addition to mitochondria, populations of ANT1 and ANT2 may reside at the apical plasma membrane and motile cilia in airway epithelia. We then evaluated the role of ANT in ciliary function given that airway hydration and ciliary motion are key roles that are dysfunctional in COPD. At the plasma membrane, ANT2 stimulates airway surface liquid hydration via ATP and protects ciliary beat frequency from cigarette smoke. ANT2 gene expression is significantly reduced in lung tissue from COPD patients (notably for GOLD stages 2 and 3). This further highlights the potential role of ANT2 modulation in protecting from metabolic defects, airway hydration, ATP regulation, and ciliary motility defects, thereby maintaining airway homeostasis.

Conclusion: Overall, combining the benefits of two model systems, human lung epithelium and Dictyostelium, provides a powerful approach for discovering new lung and airway biology while potentiating novel strategies for developing innovative therapies. The unexpected role of ANT in ciliary function may provide the clue about a key missing link in the regulation of airway surface hydration, which is essential for many airway diseases including chronic obstructive pulmonary disease and cystic fibrosis.
**Poster Abstracts**

**18-A Poster:** HIF-1a-dependent miR-374 upregulation induces pathophenotypic aberrations in pulmonary vascular adventitial fibroblasts relevant to pulmonary hypertension

**Presenter:** Julia Kooser, Undergraduate Student

**Research Interest:** Bench (Basic Science)  
VMI

**Mentors:** Stephen Chan MD, PhD

**Funding Source:** AHA Undergraduate Research Fellowship

**Authors:** Julia Kooser, Miranda Culley BS, Lloyd Harvey BS, Kurt Stenmark MD, Gil Speyer PhD, Stephen Chan MD, PhD

**Introduction:** Pulmonary hypertension (PH) is characterized by increased mean pulmonary arterial pressure that culminates in right ventricular failure and death. MicroRNAs have been shown to control pathogenic mechanisms in the lung vasculature that promote PH, but those controlling adventitial fibroblast function have not been fully defined. Preliminary data using RNA sequencing (RNA-seq) on fibroblasts isolated from cattle with PH, known as brisket disease, allowed us to construct a network of differentially expressed genes to predict miRNAs exerting influence over this network, which identified a novel regulator, miR-374. Based on this, it was hypothesized upregulation of miR-374 under hypoxia induces fibroblast phenotypic changes that promote PH.

**Methods:** MicroRNA-374 expression was assessed in primary fibroblasts transfected with inhibitor RNA (siRNA) against hypoxia-inducible factor-1a (HIF-1a). TargetScan identified candidate genes under the influence of miR-374 that were also differentially expressed in the RNA-seq. Gene expression was assessed via RT-qPCR and immunoblot following transfection of miR-374 mimics and inhibitors. Phenotypic aberrations were assessed with BrdU incorporation and caspase 3/7 activity assays.

**Results:** Under hypoxia, a known trigger of PH, miR-374 was upregulated in human pulmonary artery adventitial fibroblasts (2.05-fold change ± 0.05, p < 0.05). MicroRNA-374 was downregulated with siRNA against HIF-1a (0.28-fold change ± 0.05, p < 0.01). BMP2, a ligand of BMPR2 which has been genetically linked to PH, was downregulated with mimics of miR-374 (0.46-fold change ± 0.05, p < 0.01) and upregulated with inhibitors of miR-374 under hypoxia (1.33-fold change ± 0.05, p < 0.01). Downregulation of BOLA3, a gene implicated in iron-sulfur cluster formation and metabolic activity and genetically linked to PH, was reversed with miR-374 inhibition (1.20-fold change ± 0.05, p < 0.01).

**Conclusion:** Hypoxia leads to HIF-1a-dependent miR-374 upregulation, resulting in dysregulation of BMP2 and BOLA3, genes identified as pathogenic drivers in PH but with undefined roles in pulmonary fibroblast function. Given such miR-374-dependent gene dysregulation, miR-374 may act as a driver of pathways controlled by genetic and acquired triggers in PH.
**Poster Abstracts**

**19-A Poster: CREBRF regulates cardiomyocyte bioenergetics and survival**

**Presenter:** Aneta Kowalski, Medical Student

**Research Interest:** Bench (Basic Science)  
Endocrinology and Metabolism

**Mentors:** Erin Kershaw MD

**Funding Source:** HHMI

**Authors:** Aneta Kowalski BS, Luyun Wang MD, Erin Kershaw MD

**Introduction:** Cardiovascular diseases are among the most common and devastating conditions of the modern era. A better understanding of how the heart adapts to cellular stress could improve prevention and treatment of these increasingly prevalent disorders. A GWAS in Samoans has recently identified a variant in a putative cellular stress/energy sensor (CREBRF R457Q) linked to metabolic phenotypes in humans. Furthermore, the Drosophila homolog of CREBRF has recently been implicated in cellular bioenergetics and survival in response to nutritional stress downstream of TORC1, a cellular energy sensor known to play a critical role in cardiomyocyte metabolism and function. Despite the significance of these discoveries, CREBRF and its metabolic-risk variant remain poorly characterized. The overall objective of this project is to understand how CREBRF and its metabolic risk variant influence cardiac/cardiomyocyte metabolism and function. The central hypothesis of this project is that CREBRF and its risk variant differentially regulate cardiomyocyte bioenergetics and survival via adaptive transcriptional responses to cellular stress downstream of the cellular energy sensor TORC1.

**Methods:** To test this hypothesis, we 1) characterized the expression and regulation of CREBRF in cardiomyocytes and murine heart under conditions of low and high nutritional stress / TORC1 activity, and 2) determined if CREBRF is necessary and/or sufficient to mediate cardiomyocyte bioenergetics and survival under these conditions using knockdown/out/in and overexpression approaches.

**Results:** Our results demonstrate that CREBRF is expressed and regulated (induced by nutritional stress / TORC1 inhibition, suppressed by insulin / mTORC1 activation) in H9c2 immortalized embryonic rat ventricular myoblasts and differentiated cardiomyocytes, primary neonatal murine cardiomyocytes, and murine hearts. We further demonstrate that CREBRF is required for cardiomyocyte survival, mitochondrial function, and metabolic flexibility (ability to switch between carbohydrate and lipids as energy substrates) in the above cell models. Finally, we demonstrate that CREBRF is induced in murine hearts in response to cardiac ischemia (due to transverse aortic constriction, TAC) in a diet-dependent manner. Ongoing studies are focused on systematically dissecting the pathways surrounding CREBRF that mediate these effects and to clarify the specific pathways differentially affected by the CREBRF risk variant.

**Conclusion:** Taken together, these data support the hypothesis that CREBRF regulates cardiomyocyte bioenergetics and survival in response to cellular stress downstream of TORC1. The impact of these studies, in combination with our ongoing work in human carriers of the CREBRF variant, is that understanding the contribution of CREBRF to cardiac/cardiomyocyte metabolism and function may improve diagnosis and therapy of cardiometabolic disease.
**Introduction:** The bacterial DNA damage repair pathway (also known as the SOS response) enables bacteria to survive genotoxic stress. The pathway is comprised of a network of ~40 genes, all of which are regulated by the transcriptional repressor, LexA. In the absence of DNA damage, LexA levels are maintained at a high steady-state concentration and the SOS response is repressed. Steady-state concentrations are maintained via negative autoregulation, as the lexA promoter, itself, contains multiple LexA binding sites. This feedback circuit thus balances new LexA synthesis with the inherent decay of LexA repressor activity. In the setting of DNA damage, however, LexA undergoes a self-cleavage reaction and its repressor activity plummets rapidly, which leads to both activation of the DNA repair pathway as well as an increase in new LexA synthesis. For bacteria to survive after DNA repair they must also rapidly shut-off the SOS response, since several SOS gene products are toxic; therefore, this feedback circuit is likely critical. However, the biochemical parameters which govern the behavior of the feedback circuit remain poorly characterized.

**Methods:** To address this we have analyzed the lexA promoter in plasmid based assays with site-directed mutagenesis to alter its binding kinetics with LexA. We have also engineered a series of mutant E. coli strains containing variants of the lexA promoter.

**Results:** Our site-directed mutagenesis plasmid based assays show that only two of three putative LexA binding sites are functional on the promoter and provide no evidence for cooperative binding from the two functional binding sites. The engineered strains containing variant lexA promoters display that there are alterations in LexA autoregulation due to enhancements or decrements in LexA binding. Fitness analysis of these strains in the absence and presences of genotoxic insults revealed both the range and biochemical constraints of negative feedback in the SOS system, as our mutants that lack negative feedback or have excessive feedback appear to be nonviable.

**Conclusion:** We conclude that only two of the three putative LexA binding sites are functional on the lexA promoter and find no evidence for cooperative binding from the two functional binding sites. We also conclude that any changes within these two functional binding sites affect the range and biochemical constraints of negative feedback in the SOS system. These novel results strengthen our current understanding of the biochemical parameters which govern the behavior of the entire SOS feedback circuit.
**21-A Poster:** TACC2 regulates cigarette smoke-induced DNA damage response

**Presenter:** Xiuying Li, Research Associate

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Toru Nyunoya MD

**Funding Source:** VA merit review grant

**Introduction:** Genomic and functional studies performed by us identified TACC2 as a candidate target involved in chronic obstructive pulmonary disease (COPD) pathogenesis. TACC2 is a microtubule-associated protein involved in centrosome and microtubule organization but its role in COPD has not been previously investigated.

**Methods:** We first measured TACC2 protein levels in the lung of patients with COPD at the different stages. To determine the functional role of TACC2 protein, we evaluated cigarette smoke-induced DNA damage and cytotoxicity in TACC2 deficient or overexpressing HBECs. We next determined the effects of CS on TACC2 protein stability and the molecular mechanisms of CS-induced TACC2 protein degradation. Finally, we determined if the genetic deletion of TACC2 enhances CS-induced DNA damage and emphysematous change in a mouse model.

**Results:** We found that smokers with COPD exhibit a marked decrease in TACC2 relative to smokers without COPD. TACC2 depletion impairs homologous recombination, and augments cigarette smoke (CS)-induced DNA damage and cytotoxicity in immortalized human bronchial epithelial cells (HBEC). CS significantly reduces TACC2 protein via the ubiquitin-proteasome pathway. Indeed, a proapoptotic, ubiquitin E3 ligase subunit, termed F box L7 (FBXL7), targets TACC2 for its degradation in cells. We also observed that Tacc2-/- compared to Tacc2+/+ mice when exposed to cigarette smoke exhibit emphysematous changes accompanied by DNA damage.

**Conclusion:** Our results suggest that CS destabilizes TACC2 protein in lung epithelia by the UPS leading to subsequent DNA damage, cytotoxicity and emphysema.
22-A  Poster: Identification of New Colistin-Resistance Mechanisms in Acinetobacter baumannii

Presenter: Roberta Mettus, Research III

Research Interest: Bench (Basic Science)  Infectious Diseases

Mentors: Yohei Doi MD

Funding Source: R01

Authors: Roberta Mettus BS, Christi McElheny MS, Alina Iovleva MD, Marissa Pacey BS, Daria Van Tyne MD, Jeremy Martinson PhD, Robbie Mailliard PhD, Nic Sluis-Cremer PhD, Yohei Doi MD

Introduction: Acinetobacter baumannii is a menacing nosocomial pathogen that readily develops resistance to many antibiotics. Colistin, also known as polymyxin E, is currently the last-line choice for treating infections caused by A. baumannii. This cationic peptide is attracted to the negatively charged LPS on Gram-negative bacterial membranes and acts by destabilizing and eventually permeabilizing it. Unfortunately, there is a disturbing trend of strains developing resistance to colistin in recent years. A. baumannii is known to modify its LPS in order to disrupt the initial charge interaction. The most common mechanisms implicated in this resistance strategy is upregulation of the pmrCAB operon, a two-component regulatory system, which results in increased levels of colistin resistance, but it is not known how A. baumannii deficient in pmrCAB develop colistin resistance. We therefore aimed to determine the secondary mechanisms of resistance in pmrCAB deficient strains.

Methods: Using A. baumannii strain AB5075 and its derivative transposon mutants of pmrC, pmrA, and pmrB obtained from a mutant library at the University of Washington, we generated genetically stable colistin-resistant mutants of each by exposing them to increasing concentrations of colistin. We then conducted whole genome sequencing to identify genetic changes in these mutants. We also characterized the phenotypes of these resistant mutants, including susceptibility to Gram-positive antimicrobials, in vitro growth fitness, and in vivo virulence in a Galleria mellonella model. It is also our intention to characterize LPS in the mutants by MALDI-TOF.

Results: Colistin-resistant mutants displayed mutations in mla and lpx genes, which are known to affect membrane composition and lipid biosynthesis, respectively. These mutants were susceptible to agents typically used to target Gram-positive organisms, and their morphology is distorted from typical Gram-negative rods. Furthermore, colistin-resistant mutants displayed reduced fitness in vitro and decreased virulence in vivo.

Conclusion: A. baumannii is particularly adept at evading antibiotics such as colistin. This study has demonstrated that A. baumannii develops mutations in genes that alter its membrane composition in order to survive in the presence of colistin, but that these mutations come at a fitness cost.
23-A  Poster: Functional assays in human kidney organoids

Presenter: Nicolas Montalbetti, Junior Faculty

Research Interest: Bench (Basic Science)
Renal-Electrolyte

Mentors: Thomas Kleyman MD

Funding Source: NIH subcontract

Authors: Nicolas Montalbetti PhD, Eugenel Espiritu PhD, Shaohu Sheng MD, Neil Huikriede PhD, Catherine Baty DVM, PhD, Thomas Kleyman MD

Introduction: Kidney epithelial cells play key roles in body fluid electrolyte and acid-base homeostasis by regulating fluid transport in the nephron. The mechanisms that mediate solute filtration, reabsorption, secretion and excretion in the kidney are well established. The goal of our work is to define specific functional properties of tubular epithelial cells within kidney organoids. We hypothesize that within these structures in organoids are developing tubules composed of polarized epithelia that are segmented with distinct structural features and exhibit many of the transport processes that have been described in the developing nephron, and some of the transport processes present in the mature nephron.

Methods: Kidney organoids were derived from human iPS cells generated by the Huikriede laboratory at the University of Pittsburgh. To study ion channel expression in kidney organoids we performed patch clamp recordings in dispersed cells. Using fluorescent imaging (high speed confocal and widefield) and fluorescent lectin staining to identify tubular segments, we developed preliminary approaches to measure organoid proximal tubular (PT) function in vivo. Endocytic function of PT segments was measured using both fluorescent dextran (10 kd mw) as a fluid phase marker and fluorescent albumin for ligand mediated uptake. Among assays to measure organoid redox status, we used an indirect measurement of NAD(P)H detecting autofluorescence at 350nm excitation/460nm emission.

Results: Whole cell patch clamp recordings revealed two main population of cells. The largest showed high outward current density with a small but significant (~30%) iberiotoxin-sensitive component. The second population exhibited a low outward current density with a significant (~70%) VU951-sensitive fraction but K+ currents were insensitive to iberiotoxin. In all cases, Ba2+ inhibit 85% of the total current. Cell attached patch clamp recordings revealed a K+ channel with linear I-V relationship and a conductance of 220 pS. Imaging approaches revealed discontinuity of tubular segments, but also showed evidence of focal areas of good PT function as measured by albumin uptake and relatively high NAD(P)H levels.

Conclusion: Our preliminary studies using electrophysiology suggests that kidney organoids express BK and ROMK channels –both of which are expressed in the adult nephron--in combination with other Ba2+-sensitive K+ channels. In vivo studies of kidney organoids show focal areas of good PT function. We are developing new quantitative approaches to expand the breadth of physiologic measurements applicable to kidney organoids which can be used to guide approaches to organoid development.
**Poster: Urinary potassium promotes irritative voiding symptoms and pain in a rat model of cystitis with increased urothelial permeability**

**Presenter:** Nicolas Montalbetti, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Marcelo Carattino PhD

**Funding Source:** DCI

**Authors:** Nicolas Montalbetti PhD, Sean Stocker PhD, Gerard Apodaca PhD, Sheldon Bastacky MD, Marcelo Carattino PhD

**Introduction:** Abnormalities in the urothelial barrier have been described in certain forms of cystitis and were hypothesized to contribute to irritative voiding symptoms and pain by allowing the permeation of urinary K into suburothelial tissues, which then alters afferent signaling and smooth muscle function. Here, we examined the mechanisms underlying organ hyperactivity and pain in a model of cystitis with increased urothelial permeability.

**Methods:** Cystitis was produced in female Sprague-Dawley rats by adenoviral-mediated expression of claudin-2 (Cldn2), a tight-junction protein that forms paracellular pores and increases urothelial permeability. Bladder afferent nerve activity was measured before and during intravesical instillation with saline or saline supplemented with KCl. The effect of extracellular K on bladder sensory neuron firing was examined. Visceral pain behavior, bladder function, bladder edema and lymphocytic infiltration were evaluated in rats fed a control or low K diet.

**Results:** In the presence of a leaky urothelium, intravesical K sensitizes bladder afferents and enhances their response to distension. Extracellular K concentrations above physiological levels promote sustained firing of a population of bladder sensory neurons with tetrodotoxin-sensitive action potentials. Notably, dietary K restriction, a maneuver that reduces urinary K, prevented the development of pelvic allodynia and inflammation seen in rats expressing Cldn2 in the urothelium. Most importantly, intravesical K causes and is required to maintain bladder hyperactivity in rats with increased urothelial permeability.

**Conclusion:** Our study demonstrates that in the face of a leaky urothelium, urinary K is the main determinant of afferent hyperexcitability, organ hyperactivity and pain. These findings support the notion that voiding symptoms and pain seen in forms of cystitis that coexist with urothelial barrier dysfunction could be alleviated by cutting urinary K levels.
26-A  Poster: The role of TNFSF18 in Systemic Sclerosis

Presenter: Anna Papazoglou, Clinical Fellow

Research Interest: Bench (Basic Science)
Rheumatology and Clinical Immunology

Mentors: Robert Lafyatis MD

Authors: Anna Papazoglou MD, Christina Zinger Morse BSc, Zengbiao Qi PhD, Tracy Tabib MSc, Robert Lafyatis MD

Introduction: Systemic sclerosis is an autoimmune disease of unknown etiology, where autoimmunity and vasculopathy precede fibrosis of interstitial and perivascular tissues, causing impairment of architecture and function. Among the earliest events in the pathogenesis is vascular injury at multiple sites followed by cycles of inflammation through T cell and monocyte activation and Th2 cytokine production as well as autoimmunity through B cell activation with autoantibody production. Fibroblasts are subsequently differentiated into myofibroblasts. Previous work in Lafyatis lab has identified distinct fibroblast populations in normal skin. Ongoing work in Lafyatis lab using single cell RNA sequencing has revealed heterogeneity and subpopulation expression variability of thousands of cells as each cell has a distinct expression profile. Specifically, TNFSF18 (Tumor Necrosis Factor Superfamily 18) was expressed only by systemic sclerosis fibroblasts. This study was undertaken to investigate the role of TNFSF18 in the pathophysiology of systemic sclerosis and evaluate its significance as potential target for treatment.

Methods: Immunohistochemical staining for TNFSF18 was performed, using tissue from patients with systemic sclerosis and healthy individuals to confirm the single cell RNA-sequencing data. As point of reference α-smooth muscle actin (α-SMA) was selected, which is the most commonly used marker of the differentiated myofibroblast, as well as isotype control antibody. We used enzyme-linked immunosorbent assays to investigate further the clinical correlation between TNFSF18 in serum and the relationship to the clinical phenotype of systemic sclerosis patients.

Results: There was good correlation between TNFSF18 staining and α-SMA staining in patients with high fibroblast skin score and, subsequently, high degree of fibrosis. The presence of TNFSF18 was not seen in normal skin or when isotype control was used. Enzyme-linked immunosorbent assays results demonstrated variable levels of TNFSF18 were detected in the serum of patients of both limited and diffuse cutaneous systemic sclerosis regardless of the individual skin scores.

Conclusion: TNFSF18 presence was found in skin biopsies of systemic sclerosis particularly in patients with high fibroblast skin scores, however levels in the serum of systemic sclerosis patients appear not to be directly related to disease activity. Further study of TNFSF18 in systemic sclerosis is warranted so as to achieve better understanding of its complex pathophysiology leading to fibrosis and hopefully make substantial difference in future treatment.
Thrombospondin-1 Produced By CD11b+GR1+ Cells Induce The Expression Of Anti-inflammatory Markers IL-10, Arginase-1 And The Multi-functional Nos2 In Response To Pseudomonas Aeruginosa In an Autocrine Manner

Presenter: Hernan Penaloza, Post-Doctoral Associate

Research Interest: Bench (Basic Science)

Pulmonary, Allergy and Critical Care Medicine

Mentors: Janet Lee MD

Funding Source: R01HL136143, R01HL086884

Authors: Hernan Penaloza PhD, Rick van der Geest MSc, Janet Lee MD

Introduction: Myeloid cells such as monocytes and neutrophils drive the immune response against Pseudomonas aeruginosa (PA) and are critical for clearing the pathogen following infection. Thrombospondin-1 (TSP-1) is a matricellular protein released by a variety of cells during inflammation and triggers macrophage IL-10 production during the resolution phase of experimental lung injury. During PA pneumonia, TSP-1 promotes host survival, modulates the production of several pro-inflammatory cytokines and dampens neutrophil activity. CD11b+GR1+ cells such as monocytes or neutrophils can acquire anti-inflammatory properties in the tissue microenvironment, modulate the inflammatory response and promote repair. We hypothesized that TSP-1 is produced by CD11b+GR1+ cells in response to PA14 and promote the acquisition of an anti-inflammatory phenotype.

Methods: We generated an enriched population of CD11b+GR1+ cells from bone-marrow progenitors obtained from TSP-1 deficient (Thbs1-/-) and WT mice by culturing them in the presence of G-CSF and GM-CSF. After 5 days in culture, cells underwent surface immunophenotyping by flow cytometry using CD11b, GR1, Ly6G, Ly6C and F4/80 antibodies. We evaluated the ability of total CD11b+GR1+ cells to produce TSP-1 in response to PA14 (MOI=0.1), as well as their capacity to express il-10 (qRT-PCR and ELISA) and Arg-1, Nos2 (qRT-PCR).

Results: CD11b+GR1+ cells from WT and Thbs1-/- mice represented around 80% of total cells in culture. As anticipated, CD11b+GR1+ cells were comprised of a monocytic (CD11b+Ly6C+Ly6G+F4/80+) and a neutrophilic subset (CD11b+Ly6C-Ly6G+F4/80-), representing around 75% and 25%, respectively, in both WT and Thbs1-/- cell cultures. WT cells rapidly produced TSP-1 in response to PA14, with increase in Arginase-1 and Nos2 when compared to Thbs1-/- cells. WT mice showed robust IL-10 production, whereas Thbs1-/- cells failed to optimally produce IL-10 in response to PA14 infection.

Conclusion: P. aeruginosa induces IL-10 production and Arginase-1 gene expression in CD11b+GR1+ cells in a TSP-1 dependent manner. We speculate that the ability of these cells to produce TSP-1 in response to PA14 may provide an autocrine signal that shifts myeloid cell subsets to an anti-inflammatory phenotype. Funding: R01HL136143, R01HL086884.
29-A  **Poster:** Aquaporin-1 as a mediator of the iron-sulfur-dependent endothelial metabolic dysfunction in pulmonary hypertension

**Presenter:** Dror Perk, Undergraduate Student

**Research Interest:** Bench (Basic Science)  
VMI

**Mentors:** Stephen Chan MD PhD

**Authors:** Dror Perk, Miranda Culley BA, Adam Handen MS, Gil Speyer PhD, Seungchan Kim PhD, Mingxia Gu PhD, Marlene Rabinovitch MD, Stephen Chan MD PhD

**Introduction:** Iron-sulfur (Fe-S) cluster deficiency leads to pulmonary hypertension (PH). Specifically, lack of the Fe-S assembly proteins, for example frataxin (FXN), in the endothelium promotes PH development in vivo. A mutation in FXN causes Friedreich's ataxia (FRDA) and mortality is driven by hypertrophic cardiomyopathy which has been linked to PH. RNA sequencing of human pulmonary arterial endothelial cells (PAECs) following FXN knockdown showed down-regulation of aquaporin-1 (AQP1), a member of the aquaporin water channel protein family, transcript levels. Separately, variants within the AQP1 gene have been linked to increased risk of PH, yet its role within the endothelium is not well-defined. Hypothesis: Fe-S cluster assembly protein deficiency induces AQP1 down-regulation in the endothelium to promote phenotypic changes consistent with PH.

**Methods:** PAECs and endothelial cells derived from induced pluripotent stem cells (iPSC-ECs) from FRDA patients were studied. Fe-S protein expression was modulated by siRNA or treatment with hypoxia (<1% O2) and IL-1β. Phenotypic changes were assessed by RTqPCR, immunoblot, Amplex red H2O2, and MitoSOX assays.

**Results:** Hypoxia and IL-1β, PH triggers known to attenuate Fe-S cluster protein expression, decreased AQP1 expression (0.76-fold change ± 0.01 SEM, p<0.05, n=3 and 0.20 ± 0.07, p<0.05, respectively). Fe-S assembly protein-specific knockout of FXN (0.57 ± 0.10, p<0.05), NFU1 (0.18 ± 0.01, p<0.01), and ISCU (0.56 ± 0.09, p<0.05) led to reduced AQP1. In FRDA iPSC-ECs AQP1 mRNA (0.02 ± 0.003, p<0.01), and protein (0.44 ± 0.03, p<0.05) levels were down-regulated. AQP1 silencing resulted in decreased nitric oxide synthase 3 (NOS3) expression (0.48 ± 0.04, p<0.01) and increased whole-cell hydrogen peroxide and mitochondrial superoxide formation (1.24 ± 0.04, p < 0.05 and 5.28 ± 0.12, p < 0.01, n=6 respectively).

**Conclusion:** Fe-S cluster deficiency downregulated AQP1 in endothelial cells to promote decreased NOS3 expression and increased ROS formation – cellular phenotypes consistent with PH. This project may identify cases of complex genetic inheritance in PH, given the convergence of two seemingly distinct genetic predispositions – attenuated Fe-S cluster integrity and AQP1 deficiency.
**30-A Poster: Investigating VLA-4 as a PET imaging biomarker vaso-occlusive crisis in a mouse model of sickle cell disease**

**Presenter:** Lydia Perkins, Post-Doctoral Scholar

**Research Interest:** Bench (Basic Science)  
Cardiology

**Mentors:** Carolyn Anderson PhD

**Funding Source:** T32, P3HVB, P30CA047904

**Authors:** Lydia Perkins PhD, Lea Nyiranshuti PhD, Joseph Latoche BS, Lynda Little-Ihrig BS, Kathryn Day BS, Sina Tavakoli MD, PhD, Enrico Novelli MD, Carolyn Anderson PhD

**Introduction:** The debilitating and unpredictable pain of vaso-occlusive crisis (VOC) in sickle cell disease is the most common cause for patients to seek emergency medical attention. VOC evaluation is currently limited to patients’ measurement of pain intensity and reported location. There is a clinical need for quantitative imaging to improve VOC assessment and determine the best pain management strategy for each patient. VOC is a direct consequence of the adhesion of sickle erythrocytes to an inflamed, proinflammatory endothelium. Very late antigen-4 (VLA-4) mediates the adhesion, and could therefore be harnessed as a neuroimaging biomarker of VOC. The ultimate goal of this project is to validate whether the VLA-4 peptidomimetic PET tracer 64Cu-CB-TE1A1P-LLP2A can image VOC events in SCD patients. Here we investigate this tracer in a mouse model of SCD.

**Methods:** LLP2A was conjugated with PEG4 and a cross-bridge copper chelator (CB-TE1A1P) and radiolabeled with Cu-64, as previously described (Beaino et al., JNM 2014; 55:1856-63). 64Cu-PEG4-CB-TE1A1P-LLP2A (64Cu-LLP2A) was injected via tail vein in homozygous sickle Townes mice and nonsickling controls (n=5/group) at the dose of 200 µCi per animal (1mCi/µg). Baseline PET/CT images were acquired at 4 and 24 h post-injection (p.i.). After one week, all mice were challenged with i.v. injection of 0.1 µg/Kg lipopolysaccharide (LPS) to elicit inflammation and VOC, followed immediately by injection of 64Cu-LLP2A and subsequent PET/CT imaging at 4 and 24 h p.i. Standardized uptake values of femur and humerus were measured using VivoQuant software. After obtaining 24 h post-LPS images, mice were sacrificed, and organs were harvested and prepared for histology and immunofluorescence imaging.

**Results:** The sickle mice showed significant uptake of 64Cu-LLP2A post-LPS challenge in the humerus and femur, a common area of pain related to vaso-occlusion in humans. The ratio of SUV at 24 h p.i in humerus and entire femur to muscle in sickle cell mice was increased over baseline whereas the SUV ratio in the control mice did not show any significant change. In these mice, VLA-4 immunofluorescence imaging confirmed signal localization in the femur, spleen, and brain.

**Conclusion:** Increased 64Cu-LLP2A uptake in the humerus and femur, where VOC occurs, post LPS challenge in sickle mice but not in control mice, suggests localization of the tracer in areas of vaso-occlusion. Validation studies using histology and fluorescent imaging confirmed increased VLA-4 expression. These results suggest 64Cu-LLP2A imaging in patients with sickle cell disease who undergo vaso-occlusive events will be clinically important to determine the extent of disease, and possibly in patient management.
**31-A Poster:** Association between Inflammation Pathways and Phenotypes of Pulmonary Dysfunction Using Cluster Analysis in HIV-infected and uninfected Individuals

**Presenter:** Shulin Qin, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** NIH R01 HL125049, R01 HL120398, K24 HL123342 (AM)

**Authors:** Shulin Qin PhD, Lena Vodovotz, Seyed Mehdi Nouraie PhD, Meghan Fitzpatrick MD, Cathy Kessinger RN, Lawrence Kingsley PhD, Kristina Crothers MD, Laurence Huang MD, Alison Morris MD

**Introduction:** HIV-infected individuals are at risk of developing different phenotypes of chronic obstructive pulmonary disease (COPD) including airway obstruction and impairment of diffusing capacity for carbon monoxide (DLCO). Mechanisms underlying these phenotypes are unclear, but systemic inflammation may play an important role. The objectives of this study were to identify clusters of peripheral circulating inflammatory mediators associated with pulmonary function to determine associations between inflammation pathways and phenotypes of pulmonary dysfunction in HIV+ and HIV- individuals.

**Methods:** Three hundred and eighty HIV+ and 147 HIV- individuals were enrolled in this cohort. Demographic and clinical characteristics were collected via chart abstraction or participant self-report. Pulmonary function tests (PFTs) were performed in all participants. Chest computed tomographic (CT) scans were obtained in HIV+ participants. Expression levels of 17 inflammatory mediators (Th1, Th2, Th17 cytokines and chemokines) in plasma at baseline were measured by Luminex. Fourteen inflammatory mediators were selected for K-mean clustering with 3 cluster solutions in both the HIV+ and HIV- groups. We compared the demographic, PFTs and chest CT findings in the HIV+ and HIV- participants between different clusters using Kruskal-Wallis test and ANOVA.

**Results:** 93% of the HIV+ participants were receiving antiretroviral therapy (ART). More than half had a history of smoking, with higher cumulative pack-years of smoking in HIV+ participants. In the HIV+ group, cluster 3 with highest plasma levels of inflammatory mediators had significantly lower measures of FEV1%, FVC% and DLco%, higher percentage of lung voxels less than -910 or -950 HU, and higher pack year of smoking than those in Cluster 1 or Cluster 2. FEV1% and FVC%, and percentage of lung voxels less than -910 or -950 HU remained significant after adjusting for pack year of smoking. In the HIV- group, cluster 3 with highest plasma levels of inflammatory mediators had significantly lower measures of DLco% than those in Cluster 1 or Cluster 2. After adjusting for pack year of smoking, these differences remained significant. Correlation analyses results supported these findings.

**Conclusion:** Th1, Th2, Th17 inflammation pathways were associated with airway obstruction and emphysema in HIV+ individuals, but with impairment of diffusing capacity in HIV- individuals, suggesting that similar inflammation pathways are involved in different phenotypes of pulmonary dysfunction in HIV+ and HIV- individuals. Overall, these differences in association of inflammation pathways and phenotypes of pulmonary dysfunction in HIV+ and HIV- individuals suggest that personalized therapies may be needed.
**Introduction:** Proteinuric chronic kidney disease (CKD) is a major cause of progressive renal failure and has limited therapies. Nrf2 (nuclear factor erythroid 2 like 2) is a transcription factor that upregulates cytoprotective mechanisms including antioxidants and detoxifying genes. Keap1 (kelch-like ECH-associated protein 1) binds and inhibits Nrf2 under normal conditions to prevent activity. Under conditions of oxidative stress or chemical exposure, the Keap1 repressor releases Nrf2 which then initiates target gene transcription. While this might be expected to prevent disease, both preclinical and clinical data have suggested that Nrf2 could paradoxically aggravate proteinuria. We therefore hypothesized that Nrf2 activity accelerates progression of proteinuric CKD.

**Methods:** Keap1 hypomorphic mutant mice have reduced Keap1 expression and enhanced Nrf2 activity. Wild-type mice and Keap1 hypomorphs were subjected to a variety of proteinuric injuries including continuous angiotensin II infusion, adriamycin, and albumin overload models. Urinary albumin excretion was measured with ELISA, and glomerular damage assessed via assessment of foot process effacement, nephrin, and Wilms Tumor 1 (WT1). Systemic blood pressure was measured with radiotelemetry, and glomerular filtration rate (GFR) was determined with FITC-sinistrin. The synthetic triterpenoid, CDDO-Im, was used in the adriamycin model to upregulate Nrf2 activity.

**Results:** Compared to wild-type mice, Keap1 hypomorphs had significantly increased proteinuria in all disease models. This was associated with worsened podocyte foot process effacement and decreased nephrin and WT1, indicating increased glomerular injury. We could not detect a difference in GFR in the mutants to explain this difference. While there were mild elevations in the systolic, diastolic, and mean blood pressures in the Keap1 hypomorphs before and after angiotensin II infusion, the proteinuria was out of proportion to these differences. Treatment of wild-type mice with CDDO-Im enhanced Nrf2 activity but also increased mortality after adriamycin exposure.

**Conclusion:** Genetic Nrf2 upregulation significantly promotes glomerular injury and lethality in proteinuric kidney injury models. This phenomenon is partly explained by higher blood pressure in hypomorphic mice but other mechanisms likely play a role.
**Poster: Protective Role of XO in Heme Induced Cardiovascular Dysfunction**

**Presenter:** Heidi Schmidt, Graduate Student

**Research Interest:** Bench (Basic Science) 
VMI

**Mentors:** Adam Straub PhD

**Funding Source:** R01

**Authors:** Heidi Schmidt BS, Brittany Durgin PhD, Nolan Carew BS, Scott Hahn MS, Katherine Wood PhD, Eric Kelley PhD, Adam Straub PhD

**Introduction:** Excess circulating free heme is a key driver of hemolytic diseases such as sickle cell disease, malaria, and sepsis as well as a side effect of cardiac bypass and transplantation. Severe hemolysis (heme crisis) saturates heme scavenging pathways, leading to abundant circulating free heme and release of millimolar concentrations of ATP. Free heme can directly generate reactive oxygen species (ROS) and/or stimulate elevation in enzymatic sources of ROS, ultimately leading to overt tissue damage. Xanthine oxidase (XO), a key enzymatic source of ROS elevated in a number of hemolytic diseases, is involved in the purine degradation pathway and generates ROS as a byproduct of hypoxanthine and xanthine oxidation. Therefore, we sought to investigate the role of XO in heme crisis. We hypothesized that XO plays a harmful role in heme crisis via increased production of ROS resulting in vascular damage.

**Methods:** We developed a novel heme crisis model in which C57BL6/J mice were injected with two identical doses of hemin (0-100 umol/kg), one hour apart and monitored for 24 hours to quantify survival and pathologic changes. Heme crisis induced damage was evaluated with H&E, qRT-PCR of inflammatory markers, and hematological analysis. Plasma XO activity was evaluated by high performance liquid chromatography. To examine the role of XO, the experiment was repeated, but mice were pretreated with febuxostat, an XO inhibitor, (10 mg/kg/day) for 5 days prior to hemin injection. UV-Vis spectrophotometry was used to measure heme degradation by XO in vitro.

**Results:** Hemin dose dependently impacted survival, beginning with 87.5% survival at 50 umol/kg and 0% survival by 100 umol/kg hemin. At 50 umol/kg hemin, hematological analysis suggested additional hemolysis, and platelet activation. This dose showed increased levels of pro-inflammatory markers, and signs of hemorrhaging and overall tissue damage in the liver and lung. These injury markers correlated with a 20-fold increase in plasma XO activity at 50 umol/kg hemin. Surprisingly, febuxostat pre-treatment increased and accelerated death after hemin injection. Additionally, pro-inflammatory markers were exacerbated, and tissue damage was observed at lower doses than the non-febuxostat treated mice. Incubation of purified XO and either of its substrates with hemin resulted in decreased absorbance, suggestive of heme degradation.

**Conclusion:** In conclusion, heme crisis induces significant XO release into plasma and causes death dose-dependently; however, contrary to current dogma, XO may have a protective role during heme crisis via its ability to serve as a secondary source of heme degradation following saturation of canonical pathways.
Introduction: PINK1/Parkin-dependent mitophagy is a mitochondrial stress responsive pathway that helps maintain a healthy mitochondrial network. In this pathway, the PINK1 kinase is activated specifically on damaged mitochondria and recruits the cytosolic E3 ligase Parkin to mitochondria to promote autophagic elimination of damaged mitochondria. Both PINK1 and Parkin were identified as causal genes mutated in familial recessive early-onset parkinson disease (PD), suggesting that the impairment of PINK1/Parkin-mediated mitophagy may explain one of the pathogenic defects leading to PD. Importantly, this stress signaling pathway is triggered by the PINK1 accumulation on the damaged mitochondria. PINK1 accumulated on the surface of damaged mitochondria communicates with cytosolic molecules like Parkin in order to signal mitochondrial damage to the cytosol. Thus, the exploring of stress-dependent PINK1 accumulation mechanisms yields a stress sensing mechanism of mitochondria and offers strategies to pharmacologically activate the PINK1/Parkin pathway.

Methods: We knocked out several genes involved in PINK1 import regulations using genome editing techniques and examined the efficiency of stress-dependent PINK1 accumulation by expressing several PINK1 mutants including PD-related PINK1 mutants in each cell line.

Results: We identify an evolutionarily-conserved cluster of negatively-charged amino acid residues just C-terminal to the PINK1 transmembrane domain as an important motif for stress-dependent PINK1 accumulation. It has been considered that PINK1 accumulation may result from the dysfunction of Tim23 import machinery complex in damaged mitochondria, because the translocation of classic mitochondrial-targeting sequence (MTS) imported proteins through Tim23 complex is energetically driven by mitochondrial membrane potential. Despite the existence of an MTS, mitochondrial import of a PINK1 mutant lacking these negatively-charged amino acid residues was not efficiently blocked in damaged mitochondria. Some PD-related PINK1 mutants adjacent to clustered negatively-charged amino acid residues had similar defects. Whereas PINK1 is cleaved by mitochondrial protease PARL in healthy mitochondria, these PINK1 mutants that circumvented import arrest in damaged mitochondria were cleaved by another mitochondrial protease OMA1. Interestingly, Parkin recruitment by these PINK1 mutants was rescued by the suppression of OMA1, suggesting that the possible involvement of OMA1 in an alternate import pathway of PINK1 into damaged mitochondria.

Conclusion: Our findings provide unanticipated mechanistic insights into PINK1 signaling of mitochondrial damage, and a new potential druggable target for PD (Sekine et al., Mol. Cell, in press).
Introduction: Pulmonary hypertension (PH) is a disease resulting in increased right ventricular (RV) afterload, myocardial hypertrophy and ventricular remodeling. RV failure remains the main cause of mortality for PH patients, with 34-66% survival rates at 5 years post-diagnosis. Few systematic studies have aimed to characterize the effects of PH on RV function. Sacubitril/Valsartan is a dual-acting drug used to treat left ventricular failure that has shown promising outcomes in reducing the risk of death for heart failure in a large placebo-controlled trial. In this study, we investigated the response of failing RV tissue to treatment with Sacubitril/Valsartan.

Methods: Four groups of male Sprague–Dawley rats were studied: Sacubitril/Valsartan treatment, Valsartan-only treatment, PH rats with placebo treatment and Control. PH was induced via pulmonary artery banding (PAB). At three weeks post-surgery, terminal invasive hemodynamics was performed on the rats to obtain pressure-volume loops. Following hemodynamic measurements, the heart was removed and mechanical properties of the right ventricular free wall (RVFW) were assessed using a biaxial testing device. Tissue stress-strain data was further processed and mathematically modeled using established constitutive equations in order to analyze the degree of tissue stiffening and fiber remodeling.

Results: PAB results in significantly increased RV end-systolic pressures (78 mmHg for PAB vs. 24.9 mmHg for Control). Sacubitril/Valsartan significantly decreases end-systolic pressures (44 mmHg), while Valsartan alone shows no effects compared to the PAB group (85 mmHg). Equibiaxial stress-strain response of RVFW specimens reveals significantly increased tissue stiffness and anisotropy in the longitudinal direction (apex to outflow tract) due to PA banding (98.5 KPa for Control vs. 188.4 KPa for PAB) while showing no significant differences in the circumferential and coupled stiffnesses. Sac/Val treatment results in significantly lower longitudinal stiffness (94.5 KPa) than the PAB group, while no statistically significant differences were found between the PAB and Valsartan-only treatment groups (161.9 KPa).

Conclusion: While our study is still in progress, preliminary results suggest the potential of Sacubitril/Valsartan in lowering RV end-systolic pressure, preventing increased tissue stiffness in the longitudinal direction and RV remodeling.
**Poster Abstracts**

**36-A Poster:** Deficiency of growth suppressor Tuberous Sclerosis Complex 2 (TSC2) is required for stiffness-induced Yap/mTOR activation and pulmonary vascular remodeling in pulmonary hypertension

**Presenter:** Yuanjun Shen, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)

**Mentors:** Elena A. Goncharova PhD

**Funding Source:** NIH/ NHLBI R01 HL113178, R01 HL 130261, PO1 HL 103

**Authors:** Yuanjun Shen PhD, Andressa Pena BS, Dmitry A. Goncharov MS, Jeff Baust, Andres Chavez Barragan, Arnab Ray, Analise Rode, Stephen Chan PhD, Baojun Chang PhD, Ana L. Mora PhD, Tatiana V. Kudryashova PhD, Elena A. Goncharova PhD

**Introduction:** Increased proliferation and survival of pulmonary arterial vascular smooth muscle cells (PAVSMC) are important pathophysiological components of pulmonary vascular remodeling and pulmonary arterial hypertension (PAH). Tuberous Sclerosis Complex 2 (TSC2) is a growth suppressor protein – key negative regulator of mechanistic target of rapamycin complex 1 (mTORC1). The role of TSC2 in PAH is currently unknown.

**Methods:** Immunohistochemical, immunocytochemical and immunoblot analyses, cell transfection, cell count assays, DNA synthesis analysis (BrdU incorporation), TUNEL-based apoptosis assay by In Situ Cell Death Detection Kit.

**Results:** Immunohistochemical and immunoblot analyses demonstrated that TSC2 is down-regulated in small remodeled pulmonary arteries (PAs) and isolated distal PAVSMC from patients with PAH compared to controls. Pharmacological inhibition of Akt or activation of AMPK (AICAR) suppressed mTORC1-S6, but did not restore TSC2 in human PAH PAVSMC, suggesting that other mechanisms are involved. Analysis of various pro-PH factors (substrate stiffness, extracellular matrix proteins, growth factors, pro-inflammatory mediators) revealed that only culturing on stiff substrates dramatically reduced TSC2 protein levels in non-diseased human PAVSMC. This was associated with increased cell growth, which was prevented by TSC2 re-expression. Using human TSC2 construct and siRNA-based analysis, we found that TSC2 deficiency not only activated mTORC1-S6, but also up-regulated Yes-associated protein (YAP)/Taz and mTORC2-Akt, increased PAVSMC proliferation and protected from apoptosis. Further, TSC2 deficiency was responsible for increased production of fibronectin and collagen 1A1 in PAH PAVSMC. Growth of non-diseased PAVSMC on the matrices produced by PAH PAVSMC led to up-regulation of YAP/Taz, mTORC1-S6 and mTORC2-Akt and increased proliferation. Restoration of TSC2 protein levels by Sirt1 activator SRT2104 reduced Yap/Taz, fibronectin and collagen 1A1 levels, inhibited mTORC2-Akt and mTORC1-S6, suppressed cell proliferation and induced apoptosis in human PAH PAVSMCs. In addition to human specimens, TSC2 down-regulation was detected in small remodeled PAs from rats with monocrotaline- and rats and mice with SU5416/hypoxia-induced PH, suggesting that similar mechanisms are shared. Treatment of SU5416/hypoxia mice with SRT2104 at days 14-21 of experiment restored TSC2 protein levels in small PAs, and significantly reduced vascular smooth muscle remodeling, RVSP, and RV hypertrophy compared to vehicle-treated animals.

**Conclusion:** TSC2 acts as a mechanosensor and mechanotransducer, and its deficiency in PAH PAVSMC promotes activation of Yap/mTOR axis, excessive production of “diseased” extracellular matrix, VSMC remodeling and PH. The restoration of TSC2 may be considered as a new potentially attractive therapeutic strategy to reverse pulmonary vascular remodeling and overall PH.
**37-A  Poster:** Regulation of ENaC Expression by Paraoxonase 3

**Presenter:** Shujie Shi, Junior Faculty

**Research Interest:** Bench (Basic Science)
Renal-Electrolyte

**Mentors:** Thomas Kleyman MD

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

**Authors:** Shujie Shi PhD, Stephanie Mutchler BS, Allison Marciszyn PhD, Thomas Kleyman MD

**Introduction:** The epithelial sodium channel (ENaC) mediates the rate-limiting step of Na+ uptake across the apical membrane of specific epithelia. ENaC-dependent Na+ absorption in the kidney has important roles in regulating extracellular fluid volume, extracellular [K+] and blood pressure. ENaC functional expression is tightly regulated by multiple intracellular and exogenous factors, including molecular chaperones that are implicated in key steps during ENaC biogenesis. We previously showed that ENaC activity was reduced by paraoxonase 2 (PON2) in Xenopus oocytes. PON2–mediated inhibition is associated with reduced surface expression of ENaC, suggesting a role of PON2 in regulating ENaC turnover and/or trafficking. In supporting this notion, PONs are the mammalian orthologues of MEC-6, a C. elegans ER-resident chaperone. MEC-6 is required for the proper assembly and surface expression of the touch-sensing MEC-4/MEC-10 channel in worm touch-receptor neurons. If the chaperone function is conserved between MEC-6 and mammalian PONs, we predict other members of this family will also regulate the functional expression of related ion channels.

**Methods:** The effect of PON3 on ENaC activity was assessed by measuring whole cell Na+ currents in oocytes. We performed biochemical and electrophysiological assays to address whether ENaC surface expression and channel activity is altered under conditions in which PON3 is either over-expressed or silenced in cultured epithelial cells.

**Results:** PON3 is expressed in principal cells of the distal nephron, where ENaC resides, and forms a complex with ENaC subunits when expressed in FRT cells. PON3 inhibited ENaC activity in Xenopus oocytes. Chymotrypsin-mediated ENaC activation was not altered by PON3, suggesting that PON3 does not inhibit ENaC activity by reducing channel Po. ENaC whole cell expression was reduced by PON3 in FRT cells. Interestingly, ENaC surface expression was enhanced by PON3.

**Conclusion:** Taken together, our results suggest that PON3 functions as a chaperone to regulate ENaC expression. Future studies will investigate the mechanism by which PON3 regulates ENaC functional expression as well as the potential roles of PON3 in regulating ENaC activity, blood pressure and extracellular [K+] in the PON3 KO mice.
38-A Poster: The molybdenum enzyme mARC2 functions in maintaining energy balance.

Presenter: Courtney Sparacino-Watkins, Junior Faculty

Research Interest: Bench (Basic Science) VMI

Mentors: Mark Gladwin MD

Funding Source: Pittsburgh Liver Research Center Pilot grant

Authors: Courtney Watkins PhD, Bin Sun PhD, Michael Jurczak PhD, Mark Gladwin MD

Introduction: Molybdenum is a micronutrient and vital component of human life. Epidemiological studies report that elevated molybdenum levels are associated with insulin resistance and type 2 diabetes, but the molecular basis is unknown. In humans, biologically active molybdenum exists as part of the molybdopterin enzyme cofactor. Mitochondrial amidoxime reducing component 2 (mARC2) is a novel molybdopterin enzyme with unknown function that is predicted to function in lipid metabolism. This study was conducted to determine if mARC2 can regulate insulin action or glucose metabolism.

Methods: The effect of mARC2 deletion on whole-body energy balance, glucose homeostasis and insulin sensitivity were tested using chow-fed 12-week-old male mARC2 knockout (KO) and wildtype (WT) mice. Metabolic cages were used to measure energy expenditure, activity, and feeding and drinking behavior. Glucose homeostasis was assessed by glucose tolerance test (GTT) and insulin sensitivity assessed by hyperinsulinemic euglycemic clamp. Whole-body and tissue-specific rates of glucose metabolism were measured with 1-14C-2-deoxyglucose and 3-3H-glucose during the clamp experiments.

Results: Compared to WT littermates, mARC2 KO mice had reduced body weight and decreased fat mass in association with increased feeding, activity, and energy expenditure, suggesting the effect of mARC2 deletion on energy use exceeded the effects of increased feeding. No significant differences in plasma glucose or insulin were observed following an overnight fast; however, during GTT, plasma glucose levels were modestly reduced, and plasma insulin levels were significantly reduced in the mARC2 KO mice, suggesting improved insulin sensitivity. During hyperinsulinemic euglycemic clamp, the glucose infusion rate (GIR) required to maintain euglycemia in the mARC2 KO mice was 2.5-fold greater than WT mice, reflecting increased whole-body glucose utilization and insulin sensitivity. Fasting and insulin-stimulated rates of endogenous (primarily hepatic) glucose production were similar between groups, such that increased whole-body glucose transport fully accounted for the increased glucose utilization and improved insulin sensitivity in mARC2 KO mice. Tissue-specific rates of glucose uptake were significantly increased in white adipose tissue, inguinal adipose tissue, and heart in mARC2 KO mice, but not in brown adipose tissue or skeletal muscle. Additionally, whole-body rates of glycolysis were increased in mARC2 KO mice, demonstrating that the increased glucose transport facilitated energy production as opposed to energy (glycogen) storage.

Conclusion: These data demonstrate that whole-body glucose uptake and utilization are increased in mARC2 KO mice and suggest that mARC2 may function in maintaining energy balance. Elevated molybdenum levels observed in patients with insulin resistance and type 2 diabetes may therefore reflect up-regulated mARC2 enzyme activity.
39-A Poster: Overexpression of Twist1 in COL1A2+ Cells Leads to Increased Bleomycin-induced Pulmonary Fibrosis

Presenter: Jiangning Tan, Research Scientist

Research Interest: Bench (Basic Science)
Pulmonary, Allergy and Critical Care Medicine

Mentors: Daniel Kass MD

Funding Source: NIH RO1

Authors: Jiangning Tan PhD, Justin Dutta BS, Harinath Bahudhanapati PhD, Daniel Kass MD

Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive and devastating disorder characterized by the unremitting accumulation of activated fibroblasts in the lung leading to scarring and ultimately respiratory failure. We have previously published that patients with low gene expression for the transcription factor TWIST1 have a global gene expression profile enriched with genes suggesting inflammation and T cell activation. These patients also exhibited a higher diffusing capacity for carbon monoxide (DLCO) suggesting that low expression of TWIST1 is protective. Like the human data, COL1A2-CreER-T-Twist1 fl/fl mice, deletion of Twist1 in fibroblasts was associated with accumulation of T cells, but these animals experienced enhanced bleomycin-induced pulmonary fibrosis. This led us to hypothesize that twist1 expression may serve as a critical molecular "rheostat" in experimental pulmonary fibrosis. To test this hypothesis, we performed the opposite experiment. That is, we overexpressed Twist1 in fibroblasts to determine if increased expression of Twist1 would increase pulmonary fibrosis.

Methods: Twist overexpression transgenic mice were expressed (loci separated by commas) Col1A2-CreER-T, ROSA26-rTATA-ires-EGFP, and Twist1-tetO7-luc. WT animals were Col1A2-CreER-T, ROSA26-rTATA-ires-EGFP, and Twist1 WT. In the presence of doxycycline and tamoxifen, Twist1 is expressed at higher levels in COL1A2+ cells. The mice were injured with bleomycin and collagen content was determined by the Sircol assay. Gene expression for Tnfa, Il1b, Il6, Cxcl12, and Ccl7 was measured by qPCR from cell pellets obtained from bronchoalveolar lavage (BAL).

Results: In uninjured animals, overexpression of Twist1-Luc, increased collagen content 31%, but this was not statistically significant. Compared to bleomycin-injured WT mice, overexpression of Twist1 increased collagen content 38%, P=0.01 by two way ANOVA, N=6-8. For Tnfa, Il1b, Il6, Cxcl12, and Ccl7 gene expression in the BAL cell pellets, no significant differences were observed between Twist1-Luc and Twist1-WT.

Conclusion: Twist1 overexpression in COL1A2+ cells is associated with increased bleomycin-induced pulmonary fibrosis compared to WT. Increased collagen deposition was not associated with increased gene expression for several inflammatory cytokines/chemokines from BAL cell pellets. In contrast to our published data in Twist1 KO fibroblasts, increased expression of Twist1 is associated with increased fibrosis, but this is likely dependent on a different mechanism.
**40-A Poster: IL22RA2 regulates IL-22 activity, host defense and oxidative phosphorylation genes during pneumococcal pneumonia**

**Presenter:** Giraldina Trevejo-Nunez, Junior Faculty

**Research Interest:** Bench (Basic Science)
Infectious Diseases

**Mentors:** Sarah Gaffen PhD

**Funding Source:** K01

**Authors:** Giraldina Trevejo-Nunez MD, Waleed Elsegeiny PhD, Zoe Kaplan, Kong Chen PhD, Jay Kolls MD, Sarah Gaffen PhD

**Introduction:** Community-acquired pneumonia is caused primarily by Streptococcus pneumoniae, which is responsible for 4 million illness episodes and 22,000 deaths annually in the US. Children younger than two years old and individuals older than 65 years are the most vulnerable for invasive disease. We previously published that recombinant Interleukin 22 (IL-22) plays a role in containing pneumococcal burden in the lungs and extrapulmonary tissues by increasing hepatic Complement 3 and improving bacterial phagocytosis. Lymphoid cells secrete IL-22 and the receptor is composed of IL-22Ra1 and IL-10Rbeta. In the lung, the IL-22R localizes preferentially in the upper airway epithelial cells. IL-22 also binds to a natural antagonist, known as interleukin 22 binding protein (IL-22BP) encoded by the Il22ra2 gene. In vitro, IL-22ra2 binds to IL-22 with high affinity, competing with IL-22Ra1 and neutralizing IL-22 activity. Surprisingly little is known about IL-22BP in the lung.

**Methods:** Il22ra2-/- and wild-type (WT) controls were used to assess bacterial burden upon S. pneumoniae lung infection. Lung cells were sorted for evaluation of Il22ra2 gene expression. Lung RNA sequence of total lung tissue that compared infected Il22ra2-/- versus WT cohorts was assessed for differential gene expression. CD11c+ cells were sorted from WT, Il22ra2-/-, Il22-/- and Il22ra2-/- Il22-/- (double knockout mice) to evaluate OXPHOS genes.

**Results:** Alveolar and airway epithelial cells express IL-22BP in naïve WT lungs. Il22ra2-/- mice were more resistant than controls to S. pneumoniae infection. This resistance correlated with an increase in IL-22 in lung tissue, but it was not due to differences in cellular recruitment, neutrophil phagocytosis or chemokine expression. RNA-seq analysis of total lungs of infected Il22ra2-/- and controls revealed significant downregulation of a group of genes involved in the oxidative phosphorylation (OXPHOS) pathway. In the lung immune compartment, alveolar macrophages and dendritic cells (DCs) displayed downregulation of OXPHOS genes upon infection with S. pneumoniae. The changes in OXPHOS genes seemed to be IL-22 dependent, as IL-22-/- mice had significant upregulation of OXPHOS genes during infection compared to WT, Il22ra2-/- or double knockouts. As IL-22-Ra1 has higher expression in epithelial cells, we stimulated mouse lung epithelial cell line (MLE-12) with IL-22 and the phosphorylation of STAT3 correlated with downregulation of OXPHOS genes as well.

**Conclusion:** Altogether, the data suggest that Il22ra2 counteracts IL-22 signaling in the lung, and when absent, enhanced IL-22 signaling downregulates OXPHOS genes in epithelial, alveolar macrophages and DCs. This enhanced IL-22 effect contributes to resistance to pneumococcal pneumonia.
41-A Poster: ENaC regulation by bile acids depends on specific moieties, but not on membrane permeability

Presenter: Xueping Wang, Post-Doctoral Associate

Research Interest: Bench (Basic Science)
Renal-Electrolyte

Mentors: Ossama B. Kashlan PhD

Funding Source: R01

Authors: Xueping Wang PhD, Seohyun Janice Im undergraduate, Merve Ertem undergraduate, Deidra M. Balchak BS, Nicolas Montalbetti PhD, Marcelo D. Carattino PhD, Evan C. Ray MD, Ossama B. Kashlan PhD

Introduction: The epithelial sodium channel (ENaC) mediates Na+ transport in several epithelia, including the aldosterone-sensitive distal nephron, distal colon, and biliary epithelium. Numerous factors regulate the activity of the channel, including extracellular ligands, post-translational modifications, and membrane-resident lipids. Bile acids are abundant in the biliary tree and intestinal tract, and can be elevated in the urine of patients with advanced liver disease.

Methods: We measured amiloride-sensitive currents before and after bile acids perfusion in Xenopus oocytes expressing wild type mouse ENaCs. We also determined bile acids dose dependent regulation on ENaC in a cortical collecting duct cell line.

Results: Using Xenopus oocytes, we found that bile acids both activated and inhibited mouse ENaC, dependent on the bile acid. Whether bile acids were activating or inhibiting depended on the position and stereochemistry of specific moieties. Taurine conjugated bile acids had stronger effects than their more membrane permeant unconjugated counterparts, suggesting that bile acids regulate ENaC extracellularly. Bile acids that increased ENaC currents had a hydroxyl group at position 12, facing the hydrophilic side. Bile acids that decreased ENaC currents had a hydroxyl group at position 6. Bile acid dependent activation of ENaC currents was mildly voltage-dependent. Models fitting the voltage-dependence suggest two binding sites: 1 voltage-dependent, and 1 voltage-independent. Bile acids also regulated ENaC in a cortical collecting duct cell line, mirroring results in Xenopus oocytes.

Conclusion: Our results suggest that bile acids interact directly with ENaC near the interface between the outer leaflet and the extracellular solution, but not dependent on membrane permeability.
**Poster: Palm Domain Hydrophobic Residues and ENaC Gating**

**Presenter:** Xueqi Wang, Graduate Student

**Research Interest:** Bench (Basic Science)
Renal-Electrolyte

**Mentors:** Thomas Kleyman MD

**Funding Source:** Xiangya scholars’ research funds

**Authors:** Xueqi Wang visiting scholar, Jiingxin Chen MD, Shaohu Sheng MD, Thomas Kleyman MD

**Introduction:** Epithelial Na+ channels (ENaCs) typically contain three homologous subunits termed α, β, and γ, mediating transepithelial Na+ transport. ENaC gating is allosterically modulated by both its extracellular and intracellular domains. Among several regions that have been implicated in regulating ENaC gating are the extracellular palm domains where three subunits interface. We previously identified a palm domain hydrophobic residue (γL511) as an important determinant of ENaC gating. Interestingly, its homologous residue in chicken ASIC1a (L414), located at the β11 and β12 linker, reportedly adapts flipped conformations in the rest (or open) and desensitized states. In this study, we investigated the roles of the γL511 homologous residues in the α and β subunits (αL531 and βF502) in regulating ENaC gating, by mutating these residues to a hydrophilic glutamine and examining channel properties in Xenopus oocytes.

**Methods:** Point mutations were introduced into human α and β ENaC cDNAs by site-directed mutagenesis. Wild type (WT) and mutant human ENaCs were expressed in Xenopus oocytes by cRNA injections. ENaC 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. ENaCs both transport Na+ and are inhibited by extracellular Na+, a response referred to as Na+ self-inhibition that reflects a reduction in channel open probability and is often used as a surrogate for ENaC gating. Na+ self-inhibition was determined by measuring the decrease in current from a peak to the steady state at -100mV (intracellular potential), elicited by a rapid increase in extracellular Na+ concentration from 1 to 110mM.

**Results:** Similar to γL511Q, both αL531Q and βF502Q significantly reduced the magnitude and speed of the Na+ self-inhibition response (p<0.01 vs WT, n=6). Oocytes expressing αL531Qβ? ENaCs also showed significantly greater amiloride-sensitive currents (relative-to-WT currents: 1.9 ± 0.2, Mean ± SE, p<0.001, n=32). However, βF502Q expressing oocytes showed the channel currents that were similar to WT (relative-to-WT currents: 0.9 ± 0.1, p>0.05, n=22).

**Conclusion:** Our results suggest that the highly conserved palm domain hydrophobic residues in three subunits have similar roles in regulating ENaC gating.
**Poster Abstracts**

**43-A Poster:** Matrix stiffening regulates a QKI-microRNA-7-YAP1/TAZ signaling axis in pulmonary vascular endothelial cells: Implications for pulmonary hypertension

**Presenter:** Chen-Shan Woodcock, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)

VMI

**Mentors:** Stephen Chan MD PhD

**Authors:** Chen-Shan Woodcock PhD, Neha Hafeez BS, Leonard Estephan BS, Gil Speyer PhD, Adam Handen MS, Seungchan Kim PhD, Thomas Bertero PhD, Stephen Chan MD PhD

**Introduction:** Pulmonary hypertension (PH) refers to a set of heterogeneous vascular diseases defined by sustained elevation of pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR) leading to right ventricular (RV) remodeling and subsequent death. Pulmonary artery stiffness contributes to the pathogenesis of PH via driving vascular remodeling. Two transcriptional coactivators involved in the Hippo pathway, Yes-associated protein 1 (YAP1) and TAZ (or WWRT1), play a critical role in pulmonary vascular cell survival and proliferation in response to mechanoactivation by stiffness of extracellular matrix (ECM). However, molecular regulators driven by pulmonary vascular stiffness in the context of YAP1/TAZ signaling in PH remain incompletely defined.

**Methods:** Primary human pulmonary arterial endothelial cells (PAECs) were cultured on soft (0.5 kPa) or stiff (50 kPa) matrix. RNA sequencing of coding and non-coding RNAs was performed along with gene set enrichment analysis (GSEA). Gene and microRNA levels were measured by Taqman RT-qPCR assay. Caspase3/7 activity assay was performed to determine apoptosis.

**Results:** In PAECs cultured on soft or stiff matrix, as determined by RNA sequencing and confirmed by RT-qPCR, stiff ECM increased the activation of YAP1/TAZ by up-regulating their target CTGF gene expression, and correspondingly decreased the expression of microRNA-7 (miR-7). Conversely, forced expression of miR-7 down-regulated expression of both YAP1 and TAZ. The biogenesis of miR-7 has been suggested to be controlled by the RNA binding protein QKI. Correspondingly, in PAECs cultured on stiff ECM, QKI expression was increased; suppression of QKI under these conditions significantly increased miR-7 expression. Finally, forced miR-7 expression induced apoptotic caspase 3/7 activity in PAECs, and this observation was consistent with GSEA of RNA sequencing data, suggesting that miR-7 modulates the apoptotic pathway.

**Conclusion:** Via QKI activity, miR-7 is down-regulated in PAECs exposed to stiff matrix. In addition, miR-7 suppresses YAP1 expression and controls PAEC survival. These observations suggest that miR-7 may serve as a critical molecule that regulates mechanoactive YAP1/TAZ signaling and downstream PAEC pathophenotypes relevant to PH.
**Poster: PD-1+ T-regulatory cells in metastatic cancers’ pleural effusions exhibit attenuated suppressive function**

**Presenter:** Richard Wu, Clinical Fellow

**Research Interest:** Bench (Basic Science)  
Hematology/Oncology

**Mentors:** Dario Vignali PhD

**Funding Source:** T32

**Authors:** Richard Wu M.D., Ph.D., Feng Shan MSc, Ashwin Somasundaram MD, Chris Chuckran BS, Anthony Cillo PhD, Rajeev Dhupar MD, Sayali Onkar MSc, Sheryl Kunning MSc, Jessica Moskovitz MD, Tullia Bruno PhD, Dario Vignali PhD

**Introduction:** While T regulatory cells (Tregs) maintain normal immune homeostasis, they are also potent suppressors of the anti-tumor immune response within the tumor microenvironment (TME). Further, they are associated with lack of clinical response of metastatic melanoma patients treated with anti-PD-1 immunotherapy. Currently, it is not clear how the inhibitory receptor, PD-1, impact the function of Tregs in cancer patients. It is also not known whether there are other immune receptors that are co-expressed with PD-1 on Tregs in cancer.

**Methods:** We have obtained and isolated Tregs from pleural effusions from patients with metastatic solid and hematologic cancers, and benign effusions from patients with heart disease. We analyzed the differences in PD-1 expression of Tregs between cancer and non-cancer patients by high-dimensional flow cytometry (Cytek®). We also sorted Tregs from cancer patients’ pleural effusion by PD-1 expression and utilized an allogeneic microsuppression assay to determine the differences in suppressive function between each sorted PD-1+ vs. PD-1- subsets. We also performed computation bioinformatics analysis to evaluate the transcriptional circuitry in PD-1+ Tregs.

**Results:** We found that the Tregs in cancer patients’ pleural effusions express significantly higher levels of CD39 compared to non-cancer patients’ pleural effusions and normal-donor PBLs. By sorting cancer patients’ Tregs by PD-1, we observed that the PD-1- was more suppressive compared to that of the PD-1+ subset. PD-1+ Treg subset, however, was more proliferative compared to the PD-1- Treg subset, and expressed significantly higher levels of a co-stimulatory receptor (Inducible Co-Stimulator, ICOS), and a membrane-bound ectoenzyme (CD39). We also discovered possible co-regulation of PD-1 and CD39 by transcription factors (Egr1, Stat-1) in cancer-associated Tregs in head/neck cancer patients.

**Conclusion:** Our study indicates that the PD-1-expressing “dysfunctional” Tregs are enriched in the TME, likely due to local tumor factors such as chronic TCR stimulation. Despite PD-1+ Tregs’ increased proliferation, their suppressive function is attenuated possibly due to decreased survival or negative effect from the increased expression of CD39/purinergic metabolic pathway. Thus, we hypothesize that the PD-1 expression, together with CD39, may impact cancer patients’ Treg function and can be potentially important immune biomarkers.
**Poster: SGLT2 inhibition restores mitochondrial metabolic flexibility in heart and is associated with reduced ischemia-induced cardiac injury.**

**Presenter:** Bingxian Xie, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)
Endocrinology and Metabolism

**Mentors:** Michael Jurczak PhD

**Funding Source:** Institutional funds

**Authors:** Bingxian Xie PhD, Wesley Ramirez BS, Janet Manning PhD, Brydie Huckestein BS, Byron Chuan BS, Lanping Guo MD, Jian Hu MD, Stacy Wendell PhD, Iain Scott PhD, Christopher O’Donnell PhD, Michael Jurczak PhD

**Introduction:** Sodium-glucose co-transporter type 2 (SGLT2) is expressed in the renal proximal tubule and is responsible for glucose reabsorption. SGLT2 inhibitors (SGLT2i) improve glycemia in patients with type 2 diabetes and also confer an unforeseen cardiovascular (CV) benefit; the relative risk of death from CV-related events was reduced by 38% during a recent clinical trial. SGLT2i affected fatalities more than events, and reduced all categories of CV-related death, suggesting a generalized mechanism of improved survival. Loss of metabolic flexibility, or the ability to switch between metabolic substrates, is a feature of obesity-associated diabetic cardiomyopathy and may contribute to ATP depletion/death during ischemia due to the inability to switch from lipid to carbohydrate oxidation. Shifting energy substrate preference in cardiomyocytes from fatty acids towards glucose may, therefore, enhance cardiac protection from diabetic cardiomyopathy.

**Methods:** We measured relative rates of cardiac-specific mitochondrial glucose and lipid oxidation (PDH flux relative to TCA or VPDH/VTCA) during fasting and hyperinsulinemia using U13C-glucose infusion. Mice fed low-fat (LF), high-fat (HF; 20 wk) and HF+SGLT2i (HF+E; 4 wk 10 mg/kg/d empagliflozin) were studied. Gene expression was measured from heart infarct, peri-infarct, and remote regions one week after non-reperfused coronary artery ligations.

**Results:** Fasting rates of VPDH/VTCA were similar between groups and reflected 20% glucose/80% lipid oxidation. Cardiac VPDH/VTCA was significantly different between groups during hyperinsulinemia and reflected 55%, 25% and 45% relative usage of glucose in LF, HF, and HF+E mice, respectively. Metabolic flexibility, or the fold change in VPDH/VTCA in response to hyperinsulinemia relative to fasting (?VPDH/VTCA), was significantly different between groups and reflected a 3.1, 1.3 and 2.2-fold increase in ?VPDH/VTCA in LF, HF, and HF+E mice. Restored metabolic flexibility in HF+E mice was associated with reduced ANP and BNP gene expression in the infarct, peri-infarct and remote heart following coronary artery ligation compared with HF mice.

**Conclusion:** These data demonstrate for the first time a specific change in cardiac mitochondrial metabolism in response to SGLT2i and suggest that metabolic remodeling (more glucose utilization) of the heart may contribute to the protective effects of SGLT2i against CV-related death.
**46-A Poster:** Single-cell RNA sequencing reveals different subsets of macrophage and dendritic cells in human skin

**Presenter:** Dan Xue, Graduate Student

**Research Interest:** Bench (Basic Science)  
Rheumatology and Clinical Immunology

**Mentors:** Robert Lafyatis MD

**Funding Source:** P50

**Authors:** DAN XUE MD, Tracy Tabib MS, Christina Morse BS, Rober Lafyatis MD

**Introduction:** Professional antigen present cells (APCs), including macrophage and dendritic cell (Mf/DC) play key roles in immune homeostasis of skin: presenting antigen, and scavenging pathogens and cell debris. However, our understanding of the heterogeneity and function of different Mf/DC subsets in the skin are yet incomplete. Analyzing digested normal human skin by single cell RNA-sequencing (scRNA-seq) without pre-purifying and culture in vitro, revealed the transcriptional landscape and heterogeneity of multiple discrete Mf/DC subsets.

**Methods:** ScRNA-seq was applied to ten enzymatically-digested human dorsal mid-forearm punch biopsies and analysis was performed with Seurat. Then gene ontology (GO) enrichment analysis and immunofluorescent staining was performed.

**Results:** Using scRNA-seq, 27,869 cells from ten dorsal mid-forearm skin samples were analyzed in Seurat and 22 distinct clusters were identified using smart local moving [SLM] clustering. One cluster highly expressed , CD1C and HLA genes, verifying as Mf/DC. Upon reanalysis of this cluster (988 cells), we identified three macrophage subsets, marked by high expression of CCR1, MARCO or TREM2; six dendritic cell subsets, marked by high expression of CXorf21, MCOLN2, CLEC9A, KIAA0101, LAMP3, or CD207; this last subset representing Langerhans cells. The KIAA0101 DC subset expressed a set of genes marking proliferation and all were in G2M phase. CD69, a marker of MCOLN2 DC, and GPR157, a marker of CXorf21 DC, were expressed by two populations in this cluster, suggesting that both of these DC populations might be proliferating in normal skin. However, the lack of broad expression of discrete DC marker genes might indicate these proliferating cells represent a progenitor population. By GO enrichment analyses, biological processes more specifically attributed to CCR1 macrophage were mostly regarding chemotaxis and migration, while MARCO macrophage processes were centered around toll-like receptor signaling and TLR6:TLR2 signaling pathway. TREM2 macrophages were endowed with functions in lipid metabolism and catabolism. Then, the three Mf subsets could be defined immunofluorescently by CCR1, MARCO, TREM2 and staining.

**Conclusion:** Using scRNA-seq, we were able to reveal transcriptional landscape and phenotypic heterogeneity of Mf/DC subsets in human skin. These data will open up more opportunities to explore distinct immune cell populations and their roles in health and pathological conditions.
47-A  **Poster:** RBPJ Signaling in Macrophages Regulates Atherosclerosis

**Presenter:** Xinyi Zhang, Medical Student

**Research Interest:** Bench (Basic Science)  
VMI

**Mentors:** Partha Dutta PhD

**Funding Source:** R01,R00

**Authors:** Xinyi Zhang (Visiting Scholar), Ganesh Modugu (Undergraduate Student), Sathish Vasamsetti PhD, Jonathan Florentin PhD, Partha Dutta PhD

**Introduction:** Atherosclerosis and its subsequent cardiovascular complications like myocardial infarction and ischemic heart failure are major causes of death in the Western world. Macrophages play a central role in the formation of atherosclerotic plaques. Our RNA sequencing analysis revealed that inflammatory macrophages express high levels of RBPJ. Since inflammatory macrophages drive atherosclerosis pathogenesis, we investigated the role of RBPJ in atherosclerosis.

**Methods:** LyzMcre/+ RBPJfl/fl mice were used to assess the role of RBPJ in macrophages. Bone marrow cells from either LyzM+/+ RBPJfl/fl or LyzMcre/+ RBPJfl/fl were transplanted in mice deficient in low density receptor (ldlr-/-) to determine the role of RBPJ in atherosclerosis. These mice were fed with a high fat diet. Flow cytometry was used to enumerate immune cell populations in different organs like aorta, blood, spleen and bone marrow. RT-PCR and ELISA were performed in bone marrow derived macrophages (BMDM) and culture supernatant of BMDM, respectively to measure cytokines. Peritonitis was induced by zymosan, and peritoneal uptake of labeled apoptotic cells was measured by flow cytometry.

**Results:** We found that the atherosclerotic plaques of mice containing RBPJ-deficient macrophages had less monocytes, especially Ly6Chigh monocytes compared to control mice. Consistently, the expression of Mcp-1, responsible for monocyte recruitment, was less in the plaques of these mice. A PCR array revealed that the level of MerTK, a key macrophage efferocytosis receptor, augmented in BMDM deficient of RBPJ. This prompted us to assess the role RBPJ in efferocytosis. In vitro efferocytosis assay demonstrated increased expression of MerTK and higher efferocytosis ability of RBPJ/-/- BMDM. In line with this finding, RBPJ/-/- peritoneal macrophages engulfed higher amount of apoptotic neutrophils, indicating improved efferocytosis in these cells.

**Conclusion:** Our data suggest that RBPJ signaling in macrophages impairs efferocytosis and promotes atherosclerosis.
**Introduction:** Musica Universalis is an ancient philosophical concept that claims the movements of celestial bodies follow mathematical equations and resonate to produce an inaudible harmony of music. Besides music, electromagnetic waves such as light and electronic signals also are presented as harmonic resonances. Despite the seemingly universal theme of harmonic resonance in various disciplines, it was not until very recently that the same harmonic resonance was discovered to also exist in biological systems. It is now appreciated that most biological systems have no homeostatic “set point”, but rather oscillate as composite rhythms consisting of a series of superimposed oscillations. These oscillations often cycle at different harmonics of the circadian rhythm and among them the ~12h oscillations are found very prevalent.

**Methods:** In this poster, I will introduce the following: 1) the development of a novel mathematical tool allowing robust identification of all superimposed oscillations from time series data in an unbiased manner.

**Results:** 2) the discovery of a cell-autonomous mammalian 12h-clock controlling 12h rhythms of central dogma information flow, independent from the circadian clock, 3) illustrating how the mammalian hepatic 12h-clock couples 12h rhythms of methionine metabolism with dynamic histone lysine 4 trimethylation (H3K4me3) epigenetic control to maintain hepatic metabolic homeostasis; 4) presenting evidence supporting the hypothesis that mammalian 12h-clock evolves from the ancient circatidal clock and 5) discussing the potential roles of the 12h-clock in regulating hepatic steatosis, aging and the possibility of 12h-clock-based chronotherapy.

**Conclusion:** We envision manipulating the mammalian 12h-clock provides novel therapeutical approaches to ameliorate aging and metabolic diseases.
**Poster:** Pseudomonas aeruginosa protease and elastase activity are common in ICU respiratory isolates

**Presenter:** Jill Zupetic, Clinical Fellow

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Janet Lee MD

**Funding Source:** NIH R01HL136143, R01HL142084, R01HL086884.

**Authors:** Jill Zupetic MD, Rebecca DeSensi MS, Yanyan Qu PhD, William Bain MD, Roberta Mettus BS, Yohei Doi MD PhD, M. Nouraie MD PhD, Janet S. Lee MD

**Introduction:** Pseudomonas aeruginosa (PA) is a common cause of lower respiratory tract infections in the ICU, and PA infection has been previously shown to be independently associated with increased ICU mortality. Limited studies exist that quantify proteolytic and elastolytic activity of PA respiratory isolates from the ICU. Whether proteolytic and/or elastolytic activity is associated with monomicrobial or polymicrobial infections, susceptibility or multi-drug resistance is not known. Given the propensity of Pseudomonas elastase to cause acute tissue injury rather than chronic infections, we hypothesized that protease and elastase activity are associated with monomicrobial infections and less antibiotic resistance.

**Methods:** A prospective screen of the first PA respiratory isolates from unique ICU patients were obtained from UPMC microbiology laboratories in a deidentified manner. PA isolates were tested in vitro for total protease and elastase activity by measuring the rates of fluorogenic casein and elastin cleavage, respectively. Protease and elastase activity were normalized to a PA reference strain (PA14) and reported as % activity: none (0%), low (1-50%), moderate (51-99%), and high (>100%). Sensitive, MDR and XDR status were defined by resistance to <3 classes, >3 classes, or >6 classes of antibiotics, respectively. Monomicrobial was defined as only PA isolates identified in the final sputum culture report and polymicrobial was defined as the presence of additional pathogens identified.

**Results:** 145 P. aeruginosa ICU respiratory isolates from discrete individuals were screened for proteolytic and elastolytic activity. 61% of PA isolates showed proteolytic activity, whereas 70% of PA isolates showed elastolytic activity. Compared to the reference PA14 strain, 35% showed low, 10% moderate, and 17% showed high protease activity. 37% showed low, 10% moderate, and 23% showed high elastase activity. The level of protease and elastase activity were highly correlated (rho =0.90). Of the PA ICU respiratory isolates examined, 29% were MDR/XDR and 40% were polymicrobial. Elastase producers were inversely associated with MDR/XDR status (52% in MDR/XDR vs. 77% in sensitive group, p=0.02). There were no differences between elastase and protease producers within monomicrobial versus polymicrobial infection.

**Conclusion:** PA elastase and protease producers are common in ICU respiratory isolates representing ~60-70% of isolates. Additionally, ~20% of these isolates are classified as high producers, when compared with a reference research strain known to induce lung tissue injury and aggravate neutrophilic inflammation in mice. There were significantly less elastase producers within the MDR/XDR strains, possibly reflecting strains associated with acute rather than persistent lower respiratory tract infections.
**50-A Poster:** The Effect of CPAP Use on Insomnia Among Persons with Type 2 Diabetes and Obstructive Sleep Apnea

**Presenter:** Lynn Baniak, Junior Faculty

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine Affiliated

**Mentors:** Patrick Strollo MD

**Authors:** Lynn Baniak PhD, Susan Sereika PhD, Zhadyra Bizhanova MPH, Charles Atwood MD, Jonna Morris PhD, Robert Stansbury MD, Patrick Strollo MD, Eileen Chasens PhD

**Introduction:** The co-occurrence of obstructive sleep apnea (OSA) and insomnia is common among persons with type 2 diabetes (T2D). Although continuous positive airway pressure (CPAP) effectively treats OSA, its effect on insomnia symptoms is unclear. This secondary analysis evaluated the impact of 12 weeks of CPAP use on change in insomnia in a T2D cohort from the Diabetes Sleep Treatment Trial (R01-DK096028).

**Methods:** The sample (N=71) was randomized to either active-CPAP (n=35) or sham-CPAP (n=36). Participants were diverse (55% male, 26% non-White) and on average 59.5±9.4 years of age with mean BMI of 36.2±6.7kg/m2 and mean A1C 7.9±0.90%. All had comorbid OSA (apnea-hypopnea index [AHI] =10). AHI was determined with ApneaLinkPlus®. CPAP use was measured using Encore Anywhere® and calculated as mean minutes of daily use over 12 weeks; sham-CPAP participants were coded as having 0 minutes of therapeutic CPAP use. Insomnia was assessed at baseline and 12 weeks using the Insomnia Severity Index (ISI). The ISI contains 7 items rated 0=none to 4=very severe, the first three items evaluate sleep onset, sleep maintenance (difficulty staying asleep), and early morning wakening problems. ISI total score ranges from 0 to 28; higher scores indicate greater insomnia. Linear regression evaluated the effect of CPAP use on change in ISI scores from baseline to 12-week follow-up adjusted for baseline score.

**Results:** Mean baseline AHI was 24.5±13.9 (moderate OSA severity). Mean ISI total score was 13.7±5.5 (subthreshold insomnia). 43.1% (n=31) were classified as having clinical insomnia (ISI total score =15). No significant differences existed between the active-CPAP and sham-CPAP groups in terms of age, race, education, and baseline BMI, A1C, ISI total score, and daytime sleepiness (Epworth Sleepiness Scale) (p=.05). The sham-CPAP group had a significantly higher baseline AHI compared to the active-CPAP group (28.1±16.6 vs 20.7±9.3, p=.02). Mean daily CPAP use over 12 weeks in the active-CPAP group was 5.11±1.7 hours. A higher mean daily use of therapeutic CPAP was associated with a greater decrease in the ISI total score from baseline to 12 weeks (b=.011, p=.012) and trends (.05=p<.10) for a greater decrease in difficulty staying asleep (b=.001, p=.080) and early awakenings (b=.001, p=.098) from baseline to 12 weeks.

**Conclusion:** Use of therapeutic CPAP of at least 5 hours per night was associated with improved insomnia symptoms in persons with T2D and OSA. Future work examining the contribution of therapeutic CPAP to improvements in insomnia symptoms are needed in larger samples.
Introduction: Sepsis is a common yet heterogeneous syndrome. Phenotypes (or groups with similar clinical characteristics) are proposed using genome wide blood expression profiles. However, no analysis has yet combined clinical and biomarker data to explore sepsis phenotypes and their differential treatment effects in randomized trials. Therefore, we aim to use both clinical and biomarker data in the Protocol-Based Care for Early Septic Shock (ProCESS) randomized trial to explore severe sepsis phenotypes and to test for heterogeneity of treatment effect by phenotype comparing usual care to protocolized early, goal directed therapy.

Methods: To identify sepsis phenotypes prior to randomization in ProCESS, we used latent class analysis of 20 clinical and biomarker variables in the subset with biomarker sampling (n=543). We used logistic regression to test for interaction between phenotype and treatment arm for 60-day inpatient mortality. We compared results to a test of treatment interaction by the highest quartile (4th) of severity illness versus the lower 3 quartiles of the APACHE3 score.

Results: We determined that a 2-class model was a better fit for the data than a one class model (VMLR p=0.01). Phenotype 1 (n=66, 12%) had increased IL-6, ICAM and bilirubin and decreased platelets relative to Phenotype 2 (n=477, 88%, Figure 1). Phenotype 1 had greater 60-day inpatient mortality compared to Phenotype 2 (41% vs 16%; p<0.001). Treatment with protocolized, early goal-directed therapy (EGDT) was associated with worse 60-day inpatient mortality compared to usual care (57.7% vs. 23.1%) in Phenotype 1 only (p value for interaction=0.05). The 60-day patient mortality was similar comparing EGDT to usual care in Phenotype 2 (15.7% vs. 16.9%). 89 patients (24.5%) were classified in the highest quartile of APACHE3 score. There was no treatment interaction comparing protocolized early, goal-directed therapy vs. usual care for the highest vs. lower APACHE 3 quartiles (p value for interaction=0.42).

Conclusion: Latent class analysis identified two severe sepsis phenotypes with distinct clinical and biomarker profiles in the ProCESS trial. Phenotype 1 has increased inflammation, organ dysfunction and worse clinical outcomes. The response to protocolized early, goal-directed therapy may differ by phenotype.
Introduction: Myositis is a rare systemic autoimmune disease that targets muscle resulting in weakness and functional limitations. There are no FDA-approved treatments for myositis as clinical trials for rare diseases are costly and enrollment is limited by participant travel and expense. Thus, well-powered myositis clinical trials require innovative enrollment strategies and utilization of emerging technologies. MyPACER (Myositis Patient Centered Tele-Research) is a University of Pittsburgh NIH-funded initiative designed to evaluate if a patient-centered, observational cohort recruited using smart technology (mobile apps, wearable devices) and telemedicine principles is an efficient way to conduct clinical studies in a rare disease such as myositis. The specific aim of this study is to determine the effectiveness of recruitment through targeted advertising on social media platforms in myositis as compared to other conventional methods using the data collected through the MyPACER study.

Methods: We propose two distinct patient-recruitment strategies. The Center-based-cohort (CBC) will utilize traditional techniques such as informing local providers to facilitate recruitment, patient flyers and university clinic recruitment of existing myositis patients. The Tele-research-cohort (TRC) will utilize targeted advertising on different social media platforms, including Facebook, Twitter and Google. Myositis physician organizations and myositis patient support groups with handles on Facebook and Twitter will also promote the study. Administrators overseeing myositis patient organizations with greater than 500 members were sent a standardized message via Facebook which included a study synopsis and a request for support. Advertisements were created with emphasis placed on consistency amongst different platforms. All advertisements will have basic analytic information collected by bit.ly (analytics website). The primary outcome measure will be enrollment rates in each cohort. Secondary outcome measures between the two cohorts include screen failure rates (i.e. comparison of patients enrolled vs. those meeting eligibility through screening criteria), screen conversion rates (comparison of those meeting screening eligibility vs. those who underwent screening), click-through rates (total number of clicks on the advertisement divided by the total number of people who saw the advertisement), and click conversion rates (how many visitors complete an action divided by the total number of visitors). Recruitment success will be compared between the different social medial platforms vs. the more traditional approaches. Data analysis will utilize the 2-sample t-test and chi-square testing.

Results: Recruitment data from March 1, 2019 to April 30, 2019 will be analyzed.

Conclusion: The use of targeted, fee-based advertisements on social media platforms will result in markedly increased subject recruitment compared to conventional recruitment strategies.
**Poster: A novel method for assessment and characterization of pancreatic pain**

**Presenter:** Anna Evans Phillips, Junior Faculty

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

**Mentors:** Dhiraj Yadav MD

**Funding Source:** American Pancreatic Association

**Authors:** Anna Evans Phillips MD, Mahya Faghih MD, Asbjorn Drewes MD, Isabelle Larsen, Dhiraj Yadav MD, Soren Olesen MD

**Introduction:** Pain is a common problem in patients with inflammatory pancreatic disorders and effective therapy remains a considerable challenge. Many patients present with evidence of abnormal processing in central pain pathways, which likely contributes to the complex pain syndromes. This has major implications for treatment, but until now methods to assess and characterize central pain processing have not been available for clinical use. We have developed a simple and clinically feasible method for the assessment and characterization of pancreatic pain based on quantitative sensory testing (QST). The aim of this study was to present this method and to derive adult normative reference values to facilitate clinical implementation.

**Methods:** This was a cross-sectional, multicenter study of 122 healthy subjects with equal gender distributions across the following age groups: 18-39 years, 40-60 years and >60 years. We recorded pain detection thresholds (PDTs) to static muscle pressure stimulations at the ‘pancreatic dermatomes’ on the upper abdomen and back (viz. dermatomes that share spinal segmental innervation with the pancreas) and at three control areas. The ratio between pancreatic and control PDTs were calculated (PDT-index) to offset interindividual differences in absolute thresholds. The PDT-index was used in conjunction with repetitive pinprick stimulations (temporal summation) applied at the abdominal pancreatic dermatome to obtain a measure of segmental hyperalgesia (a proxy of central sensitization). A conditioned pain modulation (CPM) paradigm was performed to investigate descending pain modulation. The effect of age and gender on QST assessment parameters were investigated using regression models and normative reference values were derived.

**Results:** No age or gender effects were observed for the primary QST assessment parameters (PDT-index, temporal summation and CPM). In contrast, absolute PDTs were region specific and significantly lower in women than men (all p<0.05). A PDT-index <0.75 or a temporal summation score =4 indicated segmental hyperalgesia. A CPM effect <15.2% indicated impaired descending pain modulation. The approximate time for a complete QST session was 30 minutes.

**Conclusion:** We have developed normative reference values for a clinically feasible test for the characterization of pancreatic pain in adult patients. Application of this standardized QST protocol in patients will allow providers to infer mechanisms of underlying pain modulation, which may be used to better characterize pain and to inform treatment.
**Poster Abstracts**

**55-A Poster:** Pain modulatory phenotypes differentiate chronic pancreatitis patients with distinct clinical pain profiles

**Presenter:** Anna Evans Phillips, Junior Faculty

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

**Mentors:** Dhiraj Yadav MD

**Funding Source:** American Pancreatic Association

**Authors:** Mahya Faghih MD, Anna Phillips MD, Isabelle Larsen, Asbjorn Drewes MD, Vikesh Singh MD, Dhiraj Yadav MD, Soren Olesen MD

**Introduction:** Pain is a common problem in patients with chronic pancreatitis (CP) and effective therapy remains a considerable challenge. Methods based on quantitative sensory testing (QST) provide information on pain modulation and have demonstrated promise in predicting future pain status and the efficacy of analgesics. The aims of this study were to explore the existence of CP subgroups with different pain modulatory phenotypes and to investigate associations with patients’ clinical pain and psychological profiles.

**Methods:** This was a cross-sectional, multicentre study of CP patients. Patients completed questionnaires including the modified Brief Pain Inventory short form, Hospital Anxiety and Depression Score, and measures of conditional and situational Pain Catastrophizing. Using a standardized QST protocol, we recorded pain detection thresholds (PDTs) to static muscle pressure stimulations at ‘pancreatic dermatomes’ on the upper abdomen and back (viz. dermatomes that share spinal segmental innervation with the pancreas) and at three control areas. The ratio between pancreatic and control PDTs were calculated (PDT-index) to offset interindividual differences in absolute thresholds. The PDT-index was used in conjunction with repetitive pinprick stimulations (temporal summation) applied at the abdominal pancreatic dermatome to obtain a measure of segmental hyperalgesia (a proxy of central sensitization). A conditioned pain modulation (CPM) paradigm was performed to investigate descending pain modulation. Patients were grouped based on normative QST reference values and questionnaire scores were compared across subgroups to investigate associations between patients’ pain modulatory phenotypes and clinical pain and psychological profiles.

**Results:** A total of 91 patients were enrolled in the study. Mean age was 53.1±12.7 Years, 62% were men, and 65% had alcohol and/or smoking as aetiological risk factor(s). Four distinct pain modulatory phenotypes were found: group 1 (n=34) had normal pain modulation; group 2 (n=27) had impaired CPM; group 3 (n=14) had segmental hyperalgesia; and group 4 (n=16) had impaired CPM and segmental hyperalgesia (Figure). Significant differences in average clinical pain scores, as well as BPI pain and interference scores were observed across subgroups (all p<0.05), with higher pain scores observed for patients in group 4. In contrast, anxiety, depression and pain catastrophizing scores were comparable across subgroups, implying that QST profiles were not associated with psychiatric comorbidity.

**Conclusion:** Patients with segmental hyperalgesia and impaired CPM have significantly more pain compared to their counterparts with normal QST profiles. As psychological profiles were not dependent on pain modulatory phenotypes, QST provides an unbiased mean for characterization of pain on an individual patient level. This information can be used for prognostication and tailoring of management strategies.
**Poster: Using a Protocol to Reduce Sedation is Associated with Decreased Length of Stay, Delirium, and Duration of Mechanical Ventilation in the Medical Intensive Care Unit**

**Presenter:** Lara Groetzinger, Clinical Pharmacist

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Michael Donahoe MD

**Authors:** Lara Groetzinger PharmD, Phillip Lamberty MD, Julia Hainly RN, Ian Barbash MD, Bryan McVerry MD, Burton Lee MD, Jared Chiarchiaro MD, Michael Donahoe MD, Shauna Campbell RN, Pamela Smithburger PharmD, Susan Svec RN, Susan Marshall RN

**Introduction:** Targeting a light level of sedation is recommended for mechanically ventilated (MV) patients. Continuous infusion (CI) sedatives are frequently prescribed to achieve this goal. An as-needed (PRN) sedation protocol that utilizes PRN sedatives prior to initiation of CI sedation was initiated in our Medical Intensive Care Unit (MICU).

**Methods:** Patients requiring MV for greater than 24 hours with a Riker Sedation Agitation Scale (SAS) goal of 3 or 4 were evaluated for inclusion. Patients following the MICU PRN-based sedation protocol and admitted between January 1st and December 31st 2017 were included in the PRN sedation group. These patients were compared to control patients admitted between the same dates in 2016, but did not follow the PRN protocol. Patients were excluded if they had a Riker SAS goal <2, neurologic impairment, active seizure, post cardiac arrest or overdose.

**Results:** A total of 138 patients were included in the final analysis, 64 in the PRN-based sedation group and 74 in the control group. The groups were similar in gender, weight, respiratory diagnosis, and SOFA score upon MICU admission. Patients were older in the PRN sedation group, with a median age of 67 vs. 58 years, (p=0.001). There were significantly less continuous sedatives prescribed in the PRN group, with 39% of patients in the PRN group prescribed no CI sedation during MV. Fifty-four (73%) and 49 (66%) patients in the control group received CI fentanyl and propofol, compared to 30 (47%) and 17 (27%) patients in the PRN group, respectively. Patients in the PRN group had a shorter duration of propofol infusion (0.6 vs. 2.5 days, p<0.001) and received significantly less drug per MV day (17 mg vs. 9 mg, p=0.031) compared to the control group. Duration of CI fentanyl was shorter in the PRN group, and total amount of fentanyl (CI and PRN) per MV day was also less in the PRN-based sedation group (330 mcg vs. 1140 mcg, p=0.003). Patients in the PRN group had a higher percent of delirium-free coma-free days during intubation (58% vs. 33%, p=0.016), shorter MV time (3.7 vs. 5.3 days, p=0.02) and shorter MICU length of stay (LOS) (6.4 vs. 8.6 days, p=0.01) compared to the control group. Eleven percent of patients in each group experienced an adverse event such as self-extubation or unintentional device removal.

**Conclusion:** A PRN-based sedation protocol is associated with less sedation, delirium, MV duration, and MICU LOS without an increase in adverse events. Further randomized study is needed to confirm these results.
Poster: Bone Marrow Complications in Idiopathic Pulmonary Fibrosis Lung Transplant Recipients

Presenter: Stefanie Hannan, Nurse Practitioner

Research Interest: Clinical
  Pulmonary, Allergy and Critical Care Medicine

Mentors: John McDyer MD

Funding Source: ITTC

Authors: Stefanie Hannan CRNP, Iulia Popescu PhD, Spencer Winters MD, Carlo Iasella PharmD, Hannah Mannem MD, Emily McNally BS, Vidya Sagar Hanumanthu BS, Elizabeth Lendermon MD, Grant Bullock MD, Jonathan Alder PhD, Mary Armanios MD, John McDyer MD

Introduction: The majority of idiopathic pulmonary fibrosis (IPF) patients who undergo lung transplantation have short telomeres. Because patients with short telomeres are at increased risk for bone marrow failure, we investigated the clinical requirement for bone marrow biopsy (BMbx) in a retrospective case-control cohort of lung transplant recipients (LTRs). We compared short telomere (< 10th percentile) IPF-LTRs to long telomere IPF-LTRs and age-matched non-IPF-LTR controls.

Methods: Pre-transplant hematologic data and clinical BMbx results were extracted on a retrospective cohort of 35 IPF-LTRs (28 short telomeres, 7 long telomeres) and 31 age-matched non-IPF-LTR controls (median age 63 and 61 years, respectively). Lymphocyte telomere length (TL) was measured using flow cytometry and FISH (flowFISH).

Results: A cohort of IPF-LTRs was identified at our institution and flowFISH revealed 28/35 (80%) patients had short telomeres. Among these, 11/28 underwent post-transplant BMbx (39%) compared to 3/31 (9%) of non-IPF-LTRs (Odds ratio 4.27, 95% CI: (1.031-15.34); p=0.038). Only 4 of the IPF LTRs carried germline mutations in one of the 7 telomere or telomerase genes linked to IPF: 1 likely pathologic variant in RTEL1 and 3 variants of unknown significance in PARN. A hematologic evaluation determined pancytopenia in the majority of patients (73%) as an indication for BMbx. We assessed pre-transplant hematologic parameters to determine whether these differentiated patients who required post-transplant BMbx and found that pre-transplant white blood cell counts, hemoglobin, red blood cell mean corpuscular volume, and platelet counts could not identify patients who required a BMbx.

Conclusion: Telomere length measurement may be useful in identifying patients who require a post-transplant hematologic evaluation and BMbx. Pre-transplant hematologic parameters were not associated with bone marrow complications requiring BMbx in our cohort. Further studies are needed to risk-stratify patients at risk for bone marrow complications post-lung transplant.
**Poster: Respiratory viral panel testing in intensive care units: effect on outcomes.**

**Presenter:** Gavin Harris, Clinical Fellow

**Research Interest:** Clinical Infectious Diseases

**Mentors:** Fernanda Silveira MD

**Authors:** Gavin Harris MD, Fernanda Silveira MD, Kailey Hughes MPH, David Wallace MD

**Introduction:** Acute respiratory viral illnesses cause significant morbidity and mortality and lead to high healthcare costs. Delayed viral pathogen diagnosis likely contributes to this high morbidity and mortality, including inappropriate antibiotic exposure. However it is not clear if early testing improves outcomes. Complicating matters, patient vaccination status may affect physician testing behavior for critically ill patients. This study is intended to fill in these gaps with two specific aims: to determine if, in patients admitted to intensive care units (ICUs) with an acute respiratory illness during influenza season, there is a difference in whether respiratory viral panels (RVPs) are obtained based on vaccination status, and whether obtaining an RVP leads to early antiviral administration. Secondly, this study aims to determine whether RVP testing is associated with improved outcomes.

**Methods:** Data was obtained from the US Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN), an ongoing study from 2015 to the present led by CDC. It provides an annual estimate of possible influenza-associated illness in hospitals correlated with vaccine effectiveness. Inclusion criteria for HAIVEN include: adult patients presenting with respiratory symptoms =10 days prior along with an RVP taken within the same time frame. Our project deals with patients admitted to ICUs at 3 UPMC sites: PUH/MUH, SHY, SMH. Using ICD 10 codes and CDC-defined variables, 302 patients were identified from 2015-2018.

**Results:** Mean age was 58.5 years. Eighty-six percent lived at home prior to admission and 59% had at least one hospitalization over the prior 12 months. One hundred ninety-one (63%) had a smoking history and 87% had at least one high-risk condition. Thirty-six percent who received the influenza vaccine were not tested with a clinical RVP and 38% who had not received it were also not tested. Two thirds who had 4 or more hospitalizations over the prior 12 months were not tested with an RVP (p<0.05). One third of patients who did not have RVPs done required mechanical ventilation, 30% required hemodialysis, 1 required ECMO, and 31% died in-house.

**Conclusion:** Despite the fact that most patients admitted to the ICU with acute respiratory illness were presenting from home, an overwhelming majority had comorbidities and prior hospitalizations. More patients who had pre-existing lung conditions and at least 4 prior hospitalizations were not tested with an RVP and one third of those not tested for flu had serious complications. This preliminary data suggests that current RVP testing practices are omitting the highest-risk patients. Further analysis is ongoing to determine if RVP testing leads to early antiviral administration, less antibiotic days, and decreased mortality.
59-A  **Poster:** Does neighborhood walkability and area deprivation correlate with physical activity among recently hospitalized patients with systolic heart failure and co-morbid depression?

**Presenter:** Julia Holber, Research II

**Research Interest:** Clinical
General Internal Medicine

**Mentors:** Bruce Rollman MD

**Funding Source:** NIH

**Authors:** Julia Holber BA, Yan Huang MAS, Kaleab Abebe PhD, Amy Anderson MS LPC, Bea Herbeck Belnap PhD, Bruce Rollman MD

**Introduction:** Neighborhood walkability and socioeconomic advantage have been associated with residents' level of physical activity, yet few studies examined these relationships among the medically ill. We examined this issue among recently hospitalized patients with heart failure (HF) and co-morbid depression we enrolled into an NIH-funded collaborative care trial.

**Methods:** We administered the Patient Health Questionnaire (PHQ-2) to screen inpatients with systolic HF (ejection fraction =45%) and NYHA class II-IV symptoms for depression at 8 Pittsburgh hospitals; telephoned screen-positive consented patients 2-weeks later to confirm eligibility (PHQ-9=10); and mailed eligible participants a Bodymedia armband accelerometer with instructions to wear it for 7 days and then return it to us. We classified their data as “usable” if they wore the device for ≥10 hours on 4 separate days, and linked their home address to a unique neighborhood Walk Score which measures distance to amenities (businesses, parks, etc) (www.walkscore.com), and used the University of Wisconsin’s Neighborhood Atlas to determine area deprivation index (ADI) (www.neighborhoodatlas.medicine.wisc.edu). We then calculated univariate Pearson correlation coefficients between median daily step counts and Walk Score and ADI, and calculated standardized beta coefficients using multivariable regressions with step counts adjusted for age, gender, and NYHA class.

**Results:** Of the 629 depressed study patients, 223 provided usable armband data (mean age: 64 (IQR=523-2580), 57% male, 77% Caucasian, NYHA: 28% class II, 60% class III). Overall, patients tended to be inactive (median daily steps: 1,170 (IQR=523-2,580)), and their activity varied by NYHA class (median steps: class II: 1,969, class III: 1,110, and class IV: 850 steps a day (P=0.002)), but not with neighborhood Walk Score (P=0.20) or ADI (P=0.67).

**Conclusion:** Regardless of neighborhood Walk Score or ADI, patients with systolic HF and co-morbid depression tend to be highly sedentary following hospital discharge. Future analyses will examine the longitudinal impact of Walk Scores and ADI on changes in physical activity, mood, and cardiovascular outcomes following hospital discharge to inform the development of new interventions for this patient population.
Poster Abstracts

60-A  Poster: Understanding why older adults opt out of osteoporosis clinical trials after screening

Presenter: Mary Kotlarczyk, Junior Faculty

Research Interest: Clinical
Geriatric Medicine

Funding Source: P30 AG024827

Authors: Mary Kotlarczyk PhD, Nichole Bayliss PhD, Susan Greenspan MD

Introduction: Older adults are underrepresented in clinical trials despite the need to determine therapy effectiveness in an older population. Residents of long-term care (LTC), in particular, are often excluded from clinical research due to strict inclusion criteria and transportation difficulties. Even if these barriers are removed, recruitment and retention of older adults in clinical trials are challenging.

Methods: We conducted semi-structured interviews with LTC residents who consented to be screened but subsequently opted out of participating in clinical trials of zoledronic acid or denosumab for osteoporosis. Interviews were audio-recorded, transcribed, and subjected to thematic analysis using an iterative approach. Two investigators independently coded transcripts, with consistency ensured through full adjudication. Resultant themes were then used to capture the primary reason for study refusal in a larger sample of potential participants.

Results: We interviewed 15 older adults (age 85.6±5.8, 87% female). Three central themes emerged: personal reasons, advice from others, and study-related concerns. Personal reasons that arose included being "too old," having "too many" other illnesses to manage, and a desire to not take additional medications. Some individuals felt osteoporosis was not an important health concern requiring treatment in light of their other comorbidities. Several of those interviewed withdrew participation based on the advice of health professionals, family members, or friends. Older adults also expressed study-related concerns about adverse medication effects, not being guaranteed active treatment due to randomization, and discomfort with study procedures. Using these themes, we recorded the main reason for withdrawal from 109 individuals. The primary drivers of the decision to opt out were counsel from others (27%) and personal health-related issues (21%). Fewer older adults withdrew over concerns related to medication side effects (9%), feeling "too old" (6%), or placebo group placement (3%).

Conclusion: Future studies should consider strategies to engage family and physicians in the participation process. Additionally, educating older adults about the importance of their participation in clinical trials can help address the perception that they have too many health concerns to participate.
**Poster Abstracts**

**61-A Poster:** Antiphospholipid syndrome disease severity in triple positive patients compared to double and single positive patients, a retrospective chart review

**Presenter:** Michael Macklin, Medical Student

**Research Interest:** Clinical

Hematology/Oncology

**Mentors:** Donald Woytowitz MD

**Authors:** Michael Macklin PharmD, Jansen Seheult MD, Donald Woytowitz MD

**Introduction:** Antiphospholipid syndrome (APS) is a pro-thrombotic, autoimmune mediated clinical syndrome associated with increased propensity for venous and arterial thrombosis. A significant heterogeneity seems to exist between patients with it generally being unknown what factors are useful in predicting clinical course and the need for anticoagulation. A previous review suggested that meeting more laboratory criteria may be associated with higher thrombosis risk (Lim, 2013). Criteria for antiphospholipid syndrome include a positive lupus anticoagulant (LAC), and high titers of IgG/IgM anticardiolipin (acl) and beta2-glycoprotein (b2gp) antibodies. Only one positive lab-based criteria is required for diagnosis with these patients being referred to as single, double or triple positive depending on how many of these are met. Our goal was to see if meeting more laboratory criteria was associated with higher clinical severity.

**Methods:** Our primary interest was the comparison of total number of recurrences of thrombosis while on anticoagulation/antiplatelets. Only events that took place during the lowest average follow up time was included in our analysis to equalize the time of follow-up. Our secondary interest was the time to first recurrence while on anticoagulation/antiplatelet therapy.

**Results:** 34 months was used to compare number of thromboses as this was the lowest average follow-up time. The average number of recurrences using this was 0.22/patient, 0.3/patient and 0.66/patient for the single, double and triple positive groups respectively (p=0.384). The average time to first recurrence was 9.64 months for triple, 26.76 months for double and 26.44 months for single positive (p=0.10). A significant difference was seen when comparing single positive to combined double and triple positive patients (p=0.03).

**Conclusion:** Triple positive patients did trend towards having the most recurrent thromboses though this was not statistically significant. Our secondary measure of severity, time to first recurrence was also not statistically different between the three groups though again triple positive patients clearly trended towards recurring the fastest. When combining double and triple positive groups these patients did significantly recur faster than their single positive counterparts suggesting an average double/triple positive patient will have a recurrence more quickly. This is a less clinically relevant measure then number of recurrences but does suggest there may be a different clinical course that can be stratified by number of laboratory criteria giving potential information for both prognosis and future management strategies.
Introduction: Endoscopic band ligation of colon polyps in difficult locations (e.g. diverticula) has been described in isolated case reports. The safety and efficacy of colon band ligation and band autoamputation (BLA) as a primary or adjunct technique following endoscopic mucosal resection (EMR) remains unknown.

Methods: An IRB approved retrospective study was undertaken of patients undergoing colonoscopy with BLA from 1/1/2012 to 10/30/2018 by a single endoscopist at the tertiary Pittsburgh, PA veterans affairs medical center. Data collected included patient demographics, colonoscopy findings (polyp characteristics, therapies applied, complications), pathology results, follow-up results (colonoscopy and pathology), and analyzed for technical success, complications, and clinical success (follow-up endoscopic appearance and biopsy results).

Results: 54 patients (98% male; mean age 66 years) underwent 67 colonic BLA procedures with 236 bands placed (median 2; range 1-18). A 6 band ligator (Cook Medical) was used. Indications included post EMR residual polyp banding, post EMR control of bleeding or other (scar, visible vessel, submucosal lesion, polyps located in areas of segmental colitis associated with diverticulosis), difficult polyp locations including the anal verge overlying hemorrhoids, polyps growing into the terminal ileum, and overlying the appendiceal orifice, as well as serrated polyposis syndrome (SPS) with innumerable polyps. Co- incidental polyps to post EMR BLA were banded for auto-amputation (8 patients, 13 polyps). Muscle capture in the band was evident in all the post EMR cases. Technical BLA failure occurred in 4 patients due to whole polyp BLA size >2cm (2 cases) and scarring due to prior BLA (2 patients). Pathologically confirmed incomplete eradication was noted in 9 out of 33 residual post EMR BLA patients. In total, 236 bands were placed according to following distribution: ascending colon 51, transverse colon 18, descending colon 22, and rectosigmoid colon 145. There were 2 minor complications; tenesmus (18 bands in the rectosigmoid for SAS) and post-polypectomy syndrome. Multiple BLA did lead to the subjective appearance of luminal narrowing associated with scarring. Procedure technical limitations included increased time of procedure (need for scope reinsertion with bander loaded) and decreased visibility due to bander cap. Study limitations included retrospective design, and the lack of a comparison group.

Conclusion: BLA in the colon captures muscle in the band especially apparent in the post EMR setting and likely leads to full thickness auto-amputation. The technique is safe and is a useful addition and adjunct to current polypectomy and ablation methods but is cumbersome using current devices.
Poster: "Give them the door but don’t push them through it": Family Attitudes Toward Physician Led Spiritual Care

Presenter: Laura McNamara, Medical Student

Research Interest: Clinical
General Internal Medicine

Mentors: Yael Schenker MD

Funding Source: Alan Gleitsman Student Fellowship

Authors: Laura McNamara BS, William Okoniewski BS, Scott Maurer MD, Daniel Hall MD, Krissy Moehling PhD, Yael Schenker MD

Introduction: Prior research suggests that patients and their families value religious and spiritual (R/S) support from the medical team. R/S care has been incorporated as a key component of quality, palliative care. Yet, little is known about how families perceive R/S care when provided directly by a physician. Our study aimed to understand family perceptions toward physician-led R/S care.

Methods: We utilized a qualitative study design using in-depth, semi-structured interviews. We interviewed 20 primary caregivers whose children were receiving support from palliative care at a large, urban, academic center. The interview guide focused on prior experiences and attitudes towards receiving R/S care from physicians in the hospital setting. All interviews were audio recorded, transcribed verbatim, and analyzed using constant comparative methods.

Results: Subjects were predominately white (16/20), female (19/20), and Christian (16/20), with 80% rating religion or spirituality as moderately or very important in their own lives. In analyzing the interviews, three recurrent themes emerged: 1) Most caregivers view providing R/S care as a positive sign of physician empathy, while a minority (3/20) prefer to keep R/S and medical care separate, 2) Many caregivers prefer to receive R/S care from a physician with whom they have a close relationship and/or share a faith background, 3) Caregivers preferred for physicians to open the door, but for families to lead conversations about R/S care. Furthermore, 17/20 caregivers were open to the idea of physicians asking families about their R/S background and needs. In giving advice to physicians on how to broach these topics with families, one mother stated, “Give them the door, but don’t like push them through it. Because maybe today I wouldn’t wanna talk to you about my feelings... but there might be a day that I’m feeling stronger and I might want to express to you, you know, my feelings or my faith, and um, just have you be receptive for when I feel I can open up.”

Conclusion: These data suggest that caregivers have mixed perceptions on the role of the physicians in R/S care, with most indicating that physicians must allow families to set the direction of their R/S care. Some families viewed providing R/S care as a metric of empathic care. As physicians incorporate R/S conversations into medical care, more research is needed to identify implications for the patient-family-physician relationship and, more specifically, the impact of faith discordance.
**64-A Poster:** Sarcopenia predicts mortality after Transjugular Intrahepatic Portosystemic Shunt (TIPS) placement

**Presenter:** Akshata Moghe, Clinical Fellow

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

**Authors:** Akshata Moghe MD, Josh Anderson, Yicheng Tang BS, Michael Dunn MD, Shahid Malik MD, Vinay Sundaram MD

**Introduction:** Sarcopenia is a marker of frailty and predicts mortality in cirrhotic patients. Our aim was to determine if sarcopenia predicted mortality after transjugular intrahepatic portosystemic shunt (TIPS) placement, when adjusting for Model for End-stage Liver Disease (MELD) score.

**Methods:** We retrospectively reviewed cirrhotic patients who underwent the TIPS procedure at two major transplant centers from 2003-2014. CT images were used to determine sarcopenia, using measurement of L3 skeletal muscle index compared to gender specific thresholds of =39.0 cm²/m² for women and =50.0 cm²/m² for men. A competing risk analysis was used to determine risk factors for mortality after TIPS.

**Results:** A total of 175 patients were included, of which 111 had sarcopenia and 66 did not. Median length of follow-up was 881 days (range 1-4564 days). Indications for TIPS were primarily ascites (n=91, 51.7%) and variceal bleeding (n=79, 44.8%). Sarcopenic patients had a greater proportion of males (68.5% vs 46.9%, p=0.005) and lower BMI (25.3 vs 28.9, p<0.001). Mean MELD score was similar in sarcopenic (17.3) and non-sarcopenic patients (16.6). Regarding post-TIPS outcomes, patients with sarcopenia had greater mortality than those without sarcopenia (53.3% vs 47.8%, p=0.002). In addition, subgroup analysis of patients with MELD score less than 18 (n=66) showed that there was also greater mortality in those with sarcopenia compared to those without (7.2% vs 3.9%, p=0.003). Competing risks analysis adjusting for age and MELD score revealed sarcopenia to independently predict mortality after TIPS.

**Conclusion:** Sarcopenia is associated with greater mortality after TIPS, even in patients with MELD scores less than 18. Elective TIPS should be considered cautiously in those with sarcopenia.
**Poster Abstracts**

**65-A  Poster:** Identifying potential predictive factors of sleep quality in Duchenne muscular dystrophy

**Presenter:** Jennifer Newitt, Clinical Fellow

**Research Interest:** Clinical  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Patrick Strollo Jr MD

**Funding Source:** T32

**Authors:** Jennifer L Newitt MD, Heather Gordish-Dressman PhD, Paula R Clemens MD, Patrick J Strollo Jr MD

**Introduction:** Nocturnal hypoventilation in Duchenne muscular dystrophy (DMD) is often considered to be non-obstructive in origin. Recent studies demonstrate obstructive sleep apnea commonly develops in DMD patients by twelve years of age. Patients with DMD experience more sleep disturbances compared to non-affected individuals, this association is not well characterized. Mechanical ventilation is the primary intervention utilized to improve survival in patients with DMD. Numerous studies demonstrate increasing use of non-invasive ventilation (NIV) with improved survival. Optimal timing for initiation of ventilator support has not been established. Current DMD standards of care recommend obtaining polysomnography annually once the forced vital capacity (FVC) is less than 50%. Polysomnography incurs significant demands on a patient and family, as well as costs on the healthcare system, and waiting until the FVC is less than 50% may delay diagnosis of obstructive sleep apnea. Establishing potential predictors of sleep quality may identify future methods for diagnosing sleep disturbances and timing for NIV initiation in DMD.

**Methods:** The Cooperative International Neuromuscular Research Group (CINRG) conducted a natural history study and enrolled 440 males with DMD ages 2-28 years from twenty centers in nine countries. Information was collected at baseline and annual follow-up appointments from 2006-2016 including: clinical history; anthropometrics; manual muscle testing; quantitative muscle strength; pulmonary function testing; and patient-reported outcomes/health-related quality-of-life instruments. Linear regression models were used to assess the effects of multiple predictors (including age, body weight, glucocorticoid use, FVC) on self-administered Pittsburgh Sleep Quality Index (PSQI) scores. A paired t-test was used to compare self and parent-proxy reported PSQI scores in those participants age 10-18 years.

**Results:** Analysis of the data from all visits combined demonstrated increased body weight (β=0.022, p=0.002) and decreased FVC (β=-0.647, p=0.001) are significant predictors of PSQI score after adjusting for age and glucocorticoid use. Self-reported PSQI scores in participants 11-11.9 years of age was significantly greater than the parent-proxy score (p=0.044). No significant difference was detected between patient and parent-proxy PSQI scores in participants ages 12-18 years.

**Conclusion:** Decreased FVC and increased body weight are associated with poor sleep quality in patients with DMD. Self and parent-proxy completed PSQI scores are similar in DMD patients ages 12-18 years. Continuing to identify potential predictors of sleep quality in patients with DMD will inform future clinical practice leading to earlier identification of sleep disordered breathing and management of chronic respiratory failure.
**Poster**: Lung Transplant Pulmonologists’ Views of Specialty Palliative Care for Lung Transplant Recipients.

**Presenter**: Eric Nolley, Post-Doctoral Scholar

**Research Interest**: Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors**: Yael Schenker MD

**Funding Source**: T32

**Authors**: Eric Nolley MD, Jessica Fleck MA, Dio Kavalieratos PhD, Mary Amanda Dew PhD, Matthew Morrel MD, Yael Schenker MD

**Introduction**: Lung transplant recipients face foreshortened life expectancies and frequently experience significant symptoms. They may benefit from but rarely receive SPC services. Transplant pulmonologists’ views of SPC may be key to understanding SPC utilization for this population but these have not been well characterized. The objective of this study is to (1) Examine how lung transplant pulmonologists view SPC and make decisions to refer transplant recipients to SPC and (2) identify any unique aspects of lung transplantation affecting transplant pulmonologists use of SPC.

**Methods**: We conducted semi-structured interviews with attending transplant pulmonologists at nine geographically diverse high-volume transplant centers with SPC services in the U.S. and Canada. All interviews were audio-recorded and transcribed verbatim. The multidisciplinary team developed a qualitative codebook using constant comparative methods. Two investigators coded all transcripts, with disagreements discussed and resolved by consensus.

**Results**: We interviewed 37 transplant pulmonologists. Only 2 participants had never referred a lung transplant recipient to SPC. While most participants correctly defined SPC and differentiated SPC from hospice, approximately half used SPC only when disease-directed therapies failed. This approach was associated with a perception that transplant and SPC are "not convergent paths" because transplant focuses on "survival and aggressive treatment," particularly in the first post-transplant year or when re-transplantation is possible. Participants who reported using SPC alongside disease-directed therapies were more likely to view transplant as a "palliative treatment" or a "terminal illness" with an uncertain "rollercoaster" course especially after the onset of chronic rejection.

**Conclusion**: Despite viewing SPC as more than solely end-of-life care, many transplant pulmonologists view SPC as incompatible with traditional post-transplant disease-directed therapy.
Poster Abstracts

67-A  Poster: Lung Transplantation for Patients with Cystic Fibrosis and Achromobacter Xylosoxidans in the Lung Allocation Score Era.

Presenter: Eric Nolley, Post-Doctoral Scholar

Research Interest: Clinical
                  Pulmonary, Allergy and Critical Care Medicine

Mentors: Matthew Morrell MD

Funding Source: T32

Authors: Eric Nolley MD, Keven Robinson MD, Joseph Pilewski MD, Pablo Sanchez MD, Jonathan D'Cunha MD, Matthew Morrell MD

Introduction: Lung transplantation is an accepted therapy for patients with end stage lung disease due to (CF). Up to ten percent of patients with CF are colonized with Achromobacter xylosoxidans, a gram negative organism that due to its intrinsic resistance to many antibiotics may negatively impact post-transplant outcomes.

Methods: We conducted a retrospective cohort analysis of all patients receiving lung transplantation for CF from 6/2005-2015 at the University of Pittsburgh Medical Center. Patients with Burkholderia species were excluded. General and transplant related demographics, pre and post-transplant respiratory cultures and cause of death were examined. Graft survival was measured through February 2018 or last follow-up. Descriptive statistics were used to compare baseline demographics using parametric and non-parametric tests. Survival was estimated and compared by Kaplan-Meier analysis.

Results: Twenty-nine percent (26/89) of patients had a history of achromobacter infection prior to transplantation. Pre-transplantation, patients with achromobacter had a slightly higher FEV1 (25.8 +/- 2.1 vs 22.3 +/- 0.07, p = 0.031) but trended towards requiring more mechanical ventilation (42 vs 24%, p=0.081). Compared to patients without achromobacter, there was no statistically significant difference in 1 year (0.84 vs 0.94) and 3 year survival (0.68 vs 0.84) (Figure 1, p=0.291). Of the achromobacter patients, 42 (11/26) had positive explant bronchial cultures and forty-six percent (12/26) had achromobacter isolated after transplantation. Of the 12 patients with recurrent achromobacter, only 4 had positive explant cultures. Only 1 of 11 deaths was attributable to achromobacter.

Conclusion: Lung transplantation is a viable treatment option for patients with end stage CF and a history of infection with achromobacter and these patients should be considered candidates for transplantation.
68-A  Poster: Assessment of Bone Health Status in Veterans Requiring Androgen-Deprivation Therapy for Prostate Cancer

Presenter: Mihaela Oprea, Clinical Fellow

Research Interest: Clinical Endocrinology and Metabolism

Mentors: Archana Bandi MD

Authors: Mihaela Oprea MD, Archana Bandi MD

Introduction: Prostate cancer (PC) is the most common cancer in general (25%) and Veteran (33%) population. Among PC patients with fractures, 11% have clinically silent osteoporosis (OP) and 40% have low bone mass (LBM) at start of androgen-deprivation therapy (ADT). ADT is associated with bone loss in the first year of treatment. To attain better preventive bone health care (PBHC) in this population a collaborative care protocol was initiated in 2010. Primary aim was the efficacy of protocol on quality of PBHC in PC patients receiving ADT. Secondary aims assessed incident OP and OP prevention and treatment.

Methods: Performed retrospective review of 186 PC patients on ADT 2010 - 2013. Pharmacy database query identified cohort receiving ADT agents GnRH analogue (GRA) +/- Androgen receptor blockers (ARB) and matched ADT-naive patients with pathologically confirmed PC diagnosis. We assessed demographics (age, ethnicity), Gleason score (GS) and metastatic disease (MD), fall/poor bone health risk factors (RF), fragility fracture (FFX) history, serum 25OH Vitamin D(SVD) and Dual Energy X-ray absorptiometry assessment (DXA) between 0-12 months of ADT start, frequency of vitamin D (VD) and calcium supplements (Ca), fall prevention counseling (FPC), and anti-resorptive therapy (ART) over 12 months. We excluded 59 cases due to incomplete data, h/o ADT exposure, or relocation or death prior to end of study period. Continuous measures are presented as means (+/-SD), categorical measures as frequencies and percentages (% of 127). Data analyzed using SAS 9.4.

Results: Study cohort included 127 male veterans, average (avg) age 69.7 (+/-8.6) year with 79% Caucasians, avg GS 7.8(+/-2.2), 57% fall/poor bone health (1-6 RF), 30% MD, and 13% FFX history. In this cohort, 78% received dual ADT (GRA+ARB) and 17% received ART. Of ART-receiving subjects, 91% were on dual ADT, 81% had MD with average GS of 8, and 13% had OP on DXA. Within study period, 42.5% had DXA, 24% had SVD measured. Within the cohort, none had FPC, and prescription rates were 72% for VD and 75% for Ca. In patients with h/o FFX, 80% received Ca/VD and 10% had ART. Of the 54 patients with DXA, 8.9% had LBM and 54% had normal bone mineral density. Of the newly diagnosed OP (7.4%), 75% had ART and 100% had Ca/ VD therapy.

Conclusion: As compared to current literature, our cohort had higher PBHC measures (increased DXA and SVD assessments), and improved Ca/ VD therapy rates. ART rate remained low in FFX patients but improved when OP noted on DXA. Dual ADT therapy led to higher ART use. Given the integrated healthcare system with robust electronic medical records, an automated protocol with built-in guidelines will facilitate timely identification, monitoring, and therapy of PC patients at risk of bone loss/fracture.
**70-A Poster:** Validation of Pancreatitis Activity Scoring System (Pass) in a Multicenter, International Prospective Cohort: An Intercontinental Study Through Apprentice Consortium

**Presenter:** Pedram Paragomi, Post-Doctoral Associate

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

**Mentors:** Georgios Papachristou MD

**Funding Source:** Non-funded study

**Authors:** Pedram Paragomi MD, Ioannis Pothoulakis MD, Marie Tuft MS, Amir Gougol MD, Rupjyoti Talukdar MD, Rakesh Kochhar MD, Mahesh Goenka MD, Aiste Gulla MD, Vikesh Singh MD, Jose Gonzalez MD, Bechien Wu MD, Phil Greer MSc, Anna Phillips MD, Gong Tang PhD, Georgios Papachristou MD

**Introduction:** The Pancreatitis Activity Scoring System (PASS) is a novel measure to quantify dynamic activity of acute pancreatitis (AP). The aim of this study was validate PASS in a large international prospective cohort and compare PASS trajectories based on total hospital length of stay (LOS).

**Methods:** Enrollment was conducted in 22 centers in North America, Latin America, Europe, and India between 2015-2017. PASS was calculated as the summation of organ failure (×100/organ), oral intolerance (×40), SIRS (×25/criterion), morphine equivalent dose (×5) and pain score (×5) upon admission, 24, 48, 72 hours, and on day 7. Data were imputed in subjects with 2 or less components missing. Three groups were created based on (LOS) [short (SLOS): 2-3 days, intermediate (ILOS): 3-7 days, and long (LLOS): >7 days]. Discharge PASS was defined as the last value calculated =24 hours before discharge when available. To analyze difference in PASS trajectories, changes in PASS were calculated by subtracting admission score from values at each time-point. Generalized Estimating Equations with an unstructured covariance matrix were used to compare PASS between LOS subgroups over continuous time. Distribution of PASS values was compared between subgroups via Kruskal-Wallis test.

**Results:** A total of 1451 subjects were analyzed [age, median (IQR): 48(34-63), 52% male, 80% Non-Hispanic, 49% White]. According to Revised Atlanta Classification, the cohort comprised of 976 mild (67.3%), 343 moderately-severe (23.6%) and 132 severe subjects (9.1%). Based on LOS, subjects were classified into 3 subgroups: SLOS [79 (5.4%)], ILOS [528 (36.4%)], and LLOS 844 (58.2%). In total cohort, admission PASS was 120 (94-160). Subsequently, PASS showed a consistent decline: at 24 hours [100(65-150)] and 48 hours [75 (40-130)]. The detailed PASS values for the 3 LOS subgroups are shown in Table1. Median admission PASS amongst 3 LOS groups showed no clinically meaningful difference. Overall median discharge PASS was 0 (0-15) in all available subjects. After adjustment for continents, LOS subgroups exhibited different rate of change of PASS. LLOS subjects had 15 points slower rate of PASS decline per day (p-value<.0001) and significantly-higher PASS scores at 24, 48, 72 hours from admission compared to ILOS subjects (p-value<.0001 for all 3 time-points).

**Conclusion:** This study presents the largest prospective cohort that validated the application of PASS in AP with regards to duration of hospital stay. LOS subgroups demonstrated different PASS trajectories across hospitalization period with the long LOS having the slowest PASS decline over time.
71-A  Poster: Glycemic Measures Preceding Hospital Discharge and 30-day Hospital Readmission in Patients with Diabetes

Presenter: Diana Pinkhasova, Clinical Fellow

Research Interest: Clinical Endocrinology and Metabolism

Mentors: Mary Korytkowski MD

Authors: Diana Pinkhasova MD, Neeti Patel MD, Janya Swami MD, Amy Donihi PharmD, Linda Siminerio MD, Esra Karlioglu-French MD, Kristin Delisi CRNP, Deborah Hlasnik CRNP, Li Wang MS, Daniel Rubin MD, Mary Korytkowski MD

Introduction: Hospitalized patients with diabetes (DM) represent a group at high risk for readmission. Both admission and discharge glycemic measures have been associated with risk for hospital readmission, with one study demonstrating that low but not high discharge blood glucose (BG) measures predicted hospital readmission.

Methods: The purpose of this report is to examine the association between glycemic measures 48 hours prior to discharge and readmissions at 30 days in 125 non-critically ill insulin treated patients with a secondary diagnosis of DM participating in an ongoing study examining contributors to frequency of hospital readmissions. Each patient had 8-10 BG measures which were grouped according to the following categories: all values 70-250 mg/dl (Group 1, n = 40) and =1 BG <70 and/or >250 mg/dl (Group 2, = 85).

Results: Age (64 ± 9.8 vs. 60 ± 12.2), sex (% male 52 vs. 56%), BMI (33 ± 8.9 vs. 33 ± 10 kg/m2), type of DM (% type 2 DM 95 vs. 80%), and race were similar in each group, but Group 2 patients had higher HbA1c (7.3 ± 2.8 vs. 8.2 ± 2.3%) and longer DM duration (11.8 ± 9.5 vs. 15.9 ± 10 years). The percentage of patients with =1 hospital readmission at 30 days was similar (27 vs. 24%).

Conclusion: These findings demonstrate that the majority of patients experience hypoglycemia, hyperglycemia or both preceding hospital discharge, but this did not affect risk for hospital readmissions at 30 days. The contribution of hypoglycemia and hyperglycemia as contributors to readmission risk at 30 and 90 days is being examined in a larger cohort of patients in this ongoing study.
**Poster: Admission SIRS is associated with Oral Feeding Intolerance in AP: Results From an International, Multicenter, Prospective Cohort Study.**

**Presenter:** Ioannis Pothoulakis, Visiting Scholar

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

**Mentors:** Georgios Papachristou MD

**Authors:** Ioannis Pothoulakis MD, Pedram Paragomi MD, Kwonho Jeong MS, Ooka Kohtaro MD, Xiping Tang MD, Rupiyoti Talukdar MD, Rakesh Kochar MD, Mahesh Goenka MD, Aiste Gulla MD, Vikesh Singh MD, Jose Gonzalez MD, Anna Phillips MD, Gong Tang MD, Georgios Papachristou MD, Haq Nawaz MD

**Introduction:** Oral feeding intolerance (OFI) occurs in 1 in 5 patients with acute pancreatitis (AP) and results in slow clinical recovery, poor quality of life and increased health care resource utilization. The decision to start oral refeeding is empiric and there is lack of validated criteria to assist in clinical decision making. We aim to determine simple clinical predictors of OFI.

**Methods:** Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE) is an international, multicenter, prospective cohort study including data from 22 centers. Demographic, clinical and radiologic data was collected using standardized and uniform questionnaire in a prospective manner. Severity of AP was determined using the Revised Atlanta Classification (RAC). Comorbidities were assessed using the Charleston Comorbidity Index (CCI). Patients who had initial feeding attempt by mouth were considered for inclusion in the study. OFI was defined using clinical parameters including worsening epigastric abdominal pain, nausea/emesis and increased opioid requirement following an oral feeding attempt. Various clinical parameters were investigated for their association with OFI. The timing of initial feeding attempt was stratified based on day of hospitalization. Pearson’s chi-square test was used for categorical variables, while Wilcoxon’s rank-sum test, Kruskal-Wallis test, and Fisher’s exact test were used for continuous variables.

**Results:** A total of 1,233 patients were considered for inclusion in the study; of which, 160 (12.9%) met criteria for OFI. Among demographic features younger age (45 vs. 50 years; p=0.018), male sex (61% vs. 49%; p=0.004), transfer from outside hospital (38% vs 29%; p=0.02), and CCI>=2 were associated with OFI (CCI 2, 27% vs 39%; p=0.007). With respect to clinical features, alcoholic etiology (48% vs. 30%; p<0.001) and presence of SIRS on admission (49% vs 35%; p<0.001) were associated with OFI. Subjects with OFI were more likely to develop moderate/severe AP (41% vs 24%; p<0.001), had longer hospital stay (10 vs 6 days; p<0.001). The incidence of oral feeding tolerance was similar irrespective of timing (day after hospitalization) of initial feeding attempt (85%-90%).

**Conclusion:** OFI is a not uncommon clinical problem in patients with AP. Admission SIRS is associated with OFI. Patients with SIRS on admission may require a modified protocol for oral refeeding with a longer period of NPO status followed by initiation of liquid meal with close clinical monitoring. Further research is required to develop personalized nutrition management plan in patients with AP to prevent OFI.
Poster: Clinical features of hypertriglyceridemia-induced acute pancreatitis in an international, multicenter, prospective cohort (APPRENTICE consortium)

Presenter: Ioannis Pothoulakis, Visiting Scholar

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Georgios Papachristou MD

Authors: Ioannis Pothoulakis MD, Pedram Paragomi MD, Livia Archibugi MD, Marie Tuft Student, Department of Biostatistics, Rupiyoti Talukdar MD, Rakesh Kochar MD, Mahesh Goenka MD, Aiste Gulla MD, Vikesh Singh MD, Jose Gonzalez MD, Miguel Ferreira MD, Anna Phillips MD, Gong Tang PhD, Georgios Papachristou MD, Gabriele Capurso MD

Introduction: Severe hypertriglyceridemia is an established cause of acute pancreatitis (AP). Previous data on incidence, concomitant risk factors, and severity of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) in comparison to the other etiologies is limited and mainly obtained from small, retrospective and heterogenous studies. We aim to examine the prevalence, patient characteristics, and clinical outcomes of patients with HTG-AP compared to other etiologies from a large, international prospective study.

Methods: Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE) is a global, multicenter consortium prospectively enrolling AP patients from 22 international centers (United States: 8, Europe: 5, Latin America: 6, India: 3). Data was collected via standardized questionnaires and registered in REDCap (Research Electronic Data Capture). Revised Atlanta Classification (RAC) definitions were used to determine AP severity. Patients were diagnosed with primary HTG-AP when serum triglycerides levels were >500 mg/dl in the absence of other common etiologies. Pearson chi-square test and t-test were used to compare categorical and continuous variables, respectively. Multivariable logistic regression model was used with severe/moderate condition as the outcome.

Results: Overall, 1478 patients were prospectively enrolled. HTG-AP was diagnosed in 69 patients (prevalence=4.6%), of which 33.3% were male. HTG-AP patients were younger (40.4 vs 50 years; p<0.0001), had a higher BMI (30.4 vs 27.5 kg/m2; p=0.0002), were more likely to be active alcohol users (70.6% vs 48.9%; p<0.0001), diabetic (59.4% vs 15.3%; p<0.0001), and were more likely to be enrolled on a recurrent episode of AP than during their index attack (40.6% vs 24%; p=0.002) compared to other etiologies. Median TG level was 1675 mg/dl (739-3927) in HTG-AP patients, and 133 mg/dl (91-193) in the others (p=0.0001). In respect to clinical outcomes, a significantly higher number of patients in the HTG-AP group required ICU admission (26.2% vs 16.4%; p=0.036), however length of hospital stay (8 vs 8 days; p=0.7541), and mortality (1.5% vs 2.6%; p=0.566) were similar between the two groups. Comparison of severity in HTG-AP compared to other causes with multivariable logistic regression controlling for age, gender, race, BMI, and alcohol use, showed a trend for higher severity in HTG-AP that did not reach statistical significance.

Conclusion: This multinational prospective cohort found distinct baseline characteristics in HTG-AP patients, similar to what is reported in previous smaller, retrospective studies. Furthermore, there was a trend for increased severity in the HTG-AP group, with a significantly higher rate of ICU admission.
**Introduction:** The optimal post-remission management for elderly patients with acute myeloid leukemia (AML) remains undefined. For younger patients, the use of high-dose cytarabine (HIDAC) consolidation or allogeneic hematopoietic stem cell transplant is critical in maintaining durable disease control and improving survival. However, post-remission HIDAC in patients aged >60 years is associated with higher neurotoxicity rates and decreased survival benefit. The objective of this study is to determine the outcomes of using varying doses of cytarabine as post-remission consolidation therapy in an elderly AML population.

**Methods:** We conducted a single-center retrospective analysis of AML patients aged 60 years and older treated with cytarabine as consolidation therapy at UPMC Hillman Cancer Center between January 1, 2005 and December 31, 2014. Kaplan-Meier analysis was used to estimate the survival distributions and log-rank test was used to compare survival functions from groups. Multivariate analysis was performed using Cox proportional hazard regression to determine the relationship of relapse-free survival (RFS) and overall survival (OS) to patient's age, cytogenetic risk group, AML type (primary vs secondary AML), transplant status, HIDAC dose and number of cycles.

**Results:** Out of 156 identified patients, 121 were eligible for analysis. Median age at diagnosis was 65.5 years (range 59-78) with 64% male patients. Cytogenetic abnormalities were favorable in 6%, intermediate in 71%, unfavorable in 20%, and unknown in 3%. Cytarabine was administered at a mean dose of 1.44 g/m2 (range 0.75-3.0, SD 0.84) and a median number of cycles of 4 (range 1-4). For all patients, the median RFS was 12.5 months (95% CI 9.7-15.6) and was significantly different among the cytogenetic risk groups (p=0.0008 via log-rank test): favorable-risk RFS had not been reached, intermediate-risk RFS 13.6 months (95% CI 11.0-17.3), unfavorable-risk RFS 8.3 months (95% CI 3.5-8.9). Median OS was 20.5 months (95% CI 16.4-27.1) and was significantly different among the cytogenetic risk groups (p=0.003 via log-rank test): favorable-risk OS 131.3 months (95% CI 12.9-upper limit not reached), intermediate-risk OS 25.1 months (95% CI 18.9-39.4), and unfavorable-risk OS 10.8 months (95% CI 10.4-15.8). Average HIDAC dose did not significantly correlate with RFS or OS in the model. Multivariate analysis revealed a 27% decreased rate of relapse (HR 0.73, 95% CI 0.58-0.92, p=0.008), and 24% decreased mortality rate (HR 0.76, 95% CI 0.59-0.96, p=0.024) with each additional cytarabine cycle given.

**Conclusion:** Our study supports the use of cytarabine as a tolerable and effective option for post-remission therapy in elderly AML patients.
75-A Poster: Coexistence of Alcoholic Liver Disease (ALD) and Alcoholic Pancreatitis (ALP)

Presenter: Ajay Singhvi, Clinical Fellow

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Dhiraj Yadav MD

Funding Source: Internal Funding

Authors: Ajay Singhvi MD, Bassem Matta MD, Rebecca Abromitis MLS, Andrew Althouse PhD, Gavin Arteel PhD, Ramon Bataller MD, Dhiraj Yadav MD

Introduction: Chronic alcoholism is a common cause of ALD and ALP. Subjects who drink heavily can have coexistent ALD and ALP. The frequency of this phenomenon has not been adequately addressed, and available estimates vary widely. Factors determining coexistent disease and how outcomes differ from those with individual organ involvement is largely unknown. Our primary aim was to determine robust estimates of coexistent alcoholic cirrhosis (ALC) and chronic pancreatitis (CP) by conducting a systematic review of published literature.

Methods: We searched PubMed, EMBASE, and Web of Science databases using the five concepts ALP, CP, acute pancreatitis, ALD and ALC to identify relevant studies. Inclusion criteria required that studies were published in English from 1/1965-2/2018, allowed calculation of prevalence of coexistent disease, and had sample size =25. Information was abstracted systematically from each study using a predefined data collection form. Pooled estimates were calculated using a random-effects model approach. Sensitivity analyses were performed after exclusion of autopsy studies.

Results: Of 2000 eligible studies, 29 (5 autopsy) met inclusion criteria; the majority were from Europe (59%) or North America (21%); roughly 50% were published after year 2000; and most included no or few females. More subjects were available to assess the prevalence of CP in ALC (n=2211 from 15 studies) than to calculate the prevalence of ALC in CP (n=652 from 11 studies). The pooled prevalence of CP in overall ALC was 16.2% (95% CI 10.4-24.5) and after excluding autopsy studies was 15.5% (95% CI 15.5-27.7). The pooled prevalence of ALC in CP overall was 21.5% (95% CI 12-35.6) and after excluding autopsy studies was 16.9% (95% CI 11.5-24.3). Significant heterogeneity existed among studies (I2 =65-99%). The prevalence of ALP in ALD was slightly greater than the prevalence of CP in ALC (~20% overall; 15.2% after excluding autopsy studies). The prevalence of ALD or ALC in ALP was much higher (36.6-67.8% overall; 30-39% after excluding autopsy studies).

Conclusion: Coexistent liver and pancreas disease is common in heavy alcoholics. One in five patients with ALC has coexistent CP, and a similar proportion of CP have ALC. Coexisting ALD and ALP are more frequent than late manifestations of either disease. Autopsy studies demonstrate a higher prevalence of coexistent disease, suggesting frequent occurrence of subclinical disease in one or both organs. Research is needed to understand factors leading to coexistent damage to liver and pancreas and how coexistent disease affects clinical outcomes in subjects with heavy alcohol consumption.
76-A  **Poster:** Impact of Pain on Pulmonary Function and Respiratory Symptoms in People Living with HIV

**Presenter:** Deepti Singhvi, Clinical Fellow

**Research Interest:** Clinical

Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** K24

**Authors:** Deepti Singhvi MD, Seyed Nouraie PhD, Cathy Kessinger RN, Deborah McMahon MD, Renee Weinman BA, Kristina Crothers MD, Laurence Huang MD, Jessica Bon MD, Alison Morris MD, Jessica Merlin MD

**Introduction:** In the current HIV treatment era, people living with HIV (PLWH) can have a near-normal life expectancy. However, they experience a substantial burden of comorbidities including chronic pain and obstructive airway disease (COPD). Evidence from individuals with COPD suggests that pain is associated with decreased exercise capacity and increased dyspnea. Our objective is to investigate these relationships in PLWH. We hypothesize that in PLWH, the presence of chronic pain and higher levels of pain severity are associated with increased dyspnea and decreased pulmonary function and exercise capacity.

**Methods:** We performed a cross-sectional analysis of PLWH recruited from the University of Pittsburgh HIV Lung Cohort between 2017-2018. At enrollment, participants completed a pain questionnaire to assess severity and chronicity of pain and the St. George’s Respiratory Questionnaire (SGRQ) to assess respiratory symptoms. Participants underwent pre- and post-bronchodilator spirometry along with six-minute walk test (6MWT). Association between pain severity and lung function (FEV1 % predicted, FVC % predicted), 6MWT, and SGRQ was assessed with Pearson correlation and multiple stepwise regression analysis adjusted for age, gender, and BMI.

**Results:** Of 117 PLWH, median age was 56 years with 24.8% female and 45.3% African-American. Nearly three-fourths (71.9%) had ever smoked, with 52.1% currently smoking. Overall, 22.8% met the definition of COPD (post-bronchodilator FEV1/FVC < 0.70). The median FEV1 was 89.1% predicted, and the median FVC was 90.8% predicted. The median 6MWT distance was 448.8 meters, and the median SGRQ score was 8.5. Two-thirds (66.7%) reported any pain in the past week, with 26.5% reporting chronic pain. Pain severity was correlated with reduced post-bronchodilator FEV1 % predicted (standardized beta = -0.27, p = 0.005) and reduced post-bronchodilator FVC % predicted (standardized beta = -0.25, p = 0.009). Pain severity was strongly correlated with increasing SGRQ score (r = 0.47, p = 0.00). No significant correlation was seen between pain severity and 6MWT.

**Conclusion:** In PLWH, pain is common and was associated with airflow obstruction and dyspnea. These findings suggest an opportunity to better address pain management in PLWH, which could have substantial implications for improving quality of life in this population.
77-A  Poster: The Effect Of Frailty On Mortality And Defibrillator Implantation In Older Recipients Of Cardiac Resynchronization Therapy

Presenter: Roy Sriwattanakomen, Clinical Fellow

Research Interest: Clinical Cardiology

Mentors: Samir Saba MD

Funding Source: HVI Fellow Research Grant

Authors: Roy Sriwattanakomen MD, Shahzad Ahmad MD, Don Mathew MD, Megahana Amit MD, Amit Hemadri MD, Daniel Forman MD, Samir Saba MD

Introduction: Cardiac resynchronization therapy guidelines do not distinguish between defibrillators (CRT-D) and pacemakers (CRT-P). Drivers of CRT device choice remain uncertain but may be influenced by comorbidities and frailty, particularly in older patients. We evaluated the effect of frailty on CRT device choice and mortality in older (age=75 yrs) heart failure patients.

Methods: In 470 consecutive older CRT recipients with EF=35% implanted between 2002 and 2014 (age 81±4 yrs; 71% men; 19% CRT-P), we retrospectively collected 36 dichotomous variables and summed these to create a frailty score which has been previously validated in the primary care setting as a predictor of mortality. We divided the score into quartiles of fit, mild, moderate, and severe frailty and tested its association with type of CRT device implanted (binary logistic regression) and mortality (Cox regression).

Results: Over a median follow up of 4.7 yrs, 385 (82%) patients died. Frailty quartile predicted mortality in unadjusted (HR=1.33, 95% CI 1.21-1.46) and adjusted models for ejection fraction and age (HR=1.28, 95% CI 1.16-1.41). Each successive quartile of frailty was associated with a 34% decrease in the odds of CRT-D implantation (OR=0.66, 95% CI 0.53-0.84).

Conclusion: In older CRT recipients, frailty predicts mortality and decreases the odds of CRT-D implantation. Frailty assessment in older patients may assist in appropriate CRT device choice.
78-A  Poster: Impact Of T-cell Mediated Allograft Inflammation Within First-year After Kidney Transplantation: An Analysis Of Paired Biopsies From A Single Center

Presenter: Srijan Tandukar, Clinical Fellow

Research Interest: Clinical
Renal-Electrolyte

Mentors: Rajil Mehta MD

Authors: Srijan Tandukar MD, Rajil Mehta MD, Itunu Owoyemi MD, Dana Jorgensen MPH, Puneet Sood MD, Sundaram Hariharan MD

Introduction: We evaluated the impact of Clinical and Sub-Clinical T-Cell-Mediated Rejection (TCMR) and Sub-Clinical Inflammation (SCI) within 1 year posttransplant.

Methods: Adult kidney transplant patients who underwent transplants between Jan, 2013 and Dec, 2016 and biopsies at 3&12-months were included. Patients with ABMR, BKVN and those who lost the graft within 1 year were excluded. Patients were divided into 4-groups: GR-I: No inflammation (NI) in both biopsies, GR-II: Subclinical-Inflammation (SCI) in at least 1 biopsy, GR-III: SC-TCMR in at least 1 biopsy and GR-IV: C-TCMR in at least 1 biopsy. Sum of acute (t,i,g,v) and chronic (ct,ci, cg,cv) histologic scores were compared. The outcomes measures included serum creatinine, eGFR and the burden of renal disease (AUC: serum creatinine mg*month/dL) for each group from 3 month-last follow-up. In addition, Graft-Loss and Impending Graft-Loss (eGFR<20 mL/min per 1.73 m2) were measured at last follow up upto Oct, 2018.

Results: Recipient and donor demographics, variables (ESRD cause and duration, PRA I/II, CMV/EBV status, induction, CIT, WIT) were similar across groups. The mean KDPI was significantly lower in Gr-I(NI), p=0.02. There was higher acute and chronic allograft histology scores at 3/12 months, and higher cumulative renal dysfunction (AUC) among those with C-TCMR, followed by SC-TCMR and SCI compared to NI. Combination of graft loss and impending graft loss was higher among patients with C-TCMR. There was lower KM composite graft survival for C-TCMR group.

Conclusion: C-TCMR, SC-TCMR and SCI within 1-year were associated with heightened acute and chronic allograft scores with worse renal function over follow-up. C-TCMR within 1-year post-transplant is a predictor of poor graft outcome (graft loss/impending graft loss).
79-A Poster: Associations between Symptom Burden and Unmet Existential Care Needs in Adults with Cystic Fibrosis

Presenter: Elizabeth Trandel, Medical Student

Research Interest: Clinical General Internal Medicine

Mentors: Dio Kavalieratos PhD

Authors: Elizabeth Trandel BS, Joseph Pilewski MD, Elisabeth Dellon MD, Laura Moreines MSN, CRNP, Jonathan Yabes PhD, Kwonho Jeong MS, Robert M. Arnold MD, Dio Kavalieratos PhD

Introduction: Although patients with cystic fibrosis (CF) experience high symptom burden and impaired quality-of-life, little is known about their existential distress. The objective of this analysis was to identify the prevalence of unmet existential care needs, and their relationship with symptom burden in adults with CF.

Methods: Adults with CF recruited from an academic CF center completed the Supportive Care Needs Survey-34, which measures the presence of and need for support with 34 common supportive care needs; this analysis focused on five existential care needs. Multivariable logistic regression evaluated the relationship between symptom burden, measured by the Edmonton Symptom Assessment System (ESAS) total score, and care needs, adjusting for clinical and demographic variables. ESAS total score was rescaled at six-point intervals, the minimally important difference.

Results: 164 patients (median age: 31 years; 56% male) completed the surveys. 11% of patients reported no symptom burden, 61% reported mild burden, and 28% reported moderate/severe burden. Of the needs analyzed, the most prevalent were fears about CF worsening (50%), functional limitations (43%), and uncertainty about the future (39%). Patients with moderate/severe symptom burden were significantly likelier to report needing support with all five existential care needs than patients with no or mild symptom burden (p <0.001). For each six-point increase in symptom burden, there was an increased odds of reporting need for support with each of the five existential care needs analyzed: learning to feel in control (OR=1.51; 95% CI=1.28-1.77), feelings about death and dying (1.49; 1.27-1.75), fears about their CF worsening (1.47; 1.24-1.73), uncertainty about the future (1.44; 1.24-1.68), and concerns about the worries of others (1.31; 1.14-1.50).

Conclusion: Symptom burden is associated with existential care needs among adults with CF. CF-specific palliative care support based on the prevalent unmet existential needs in this population should be developed and offered to the most burdened patients.
**Poster Abstracts**

**80-A Poster:** Pain “Burn-out” During the Natural Course is Independent of the Duration of Chronic Pancreatitis (CP)

**Presenter:** Kishore Vipperla, Clinical Fellow

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

**Mentors:** Dhiraj Yadav MD

**Funding Source:** NIH:NIDDK - Diabetes & Digestive & Kidney Disease

**Authors:** Kishore Vipperla MD, Andrew Althouse PhD, Allison Kanakis MD, Adam Slivka MA, David Whitcomb MD, Georgios Papachristou MD, Randall Brand MD, Dhiraj Yadav MD

**Introduction:** Classic natural history studies, published before year 2000, suggest two specific pain patterns in CP: patients with Type A pain have uncomplicated disease; those with Type B pain have complicated disease needing surgery to relieve pain. Pain “burn-out” during the clinical course in both groups is suggested, however data on this issue remains conflicting. Our aim was to describe the natural history of pain in a well-phenotyped cohort of CP in the modern era with specific attention to the duration of CP and role of intervention (endotherapy and/or surgery).

**Methods:** Records of 279 patients enrolled from 2000-2014 in the North American Pancreatitis Study 2 from the University of Pittsburgh were retrospectively reviewed to collect relevant data. Specific attention was paid to pain (at any time, at enrollment, during follow-up, at end of study), treatment received including narcotics, interventions, hospitalizations, diabetes, pancreatic enzyme (PERT) use, and mortality. Mean duration of observation for primary analysis calculated from the ages at first diagnosis of acute (AP) or CP to the last contact until 11/2017 was 9.4±6.7 yrs.

**Results:** Any intervention during the clinical course was required in 67.3% patients (endotherapy alone 32.6%, surgery alone 6.3%, and both 28.3%). When compared with patients in medical group, those in the intervention group were significantly (p<0.05) younger at diagnosis, had a higher prevalence of AP, RAP, diabetes and PERT use. Patients in intervention group were significantly (p<0.05) more likely to have any pain (98% vs. 75%), report severe (71% vs. 64%) pain at enrollment, have Type B pain during clinical course and require narcotics as outpatient. Although attenuation of pain was observed in a subset, 34% of medical group and 60% of intervention group still had pain at the end of study. On regression analysis, after controlling for demographics, smoking, etiology, diabetes, PERT use, and duration of CP, the odds of being in pain at any time (OR 14.4, 95% CI 4.5-46.5) and at the end of study (OR 2.6, 95% CI 1.43-4.72) was significantly higher in the intervention group when compared with medical group. Moreover, there was no association between the duration of CP with any pain, severe pain at enrollment and pain at the end of study period.

**Conclusion:** Patients who require an intervention for CP have more aggressive phenotype than patients managed medically. Although pain burn-out is seen in a subset, patients achieve pain relief at different times, which is independent of the duration of disease. These data suggest that better strategies are needed for pain assessment and to identify patients likely to benefit from interventions for CP.
**81-A Poster:** Identifying Vulnerable Plaque in Rheumatoid Arthritis using Novel Microbubble Contrast-Enhanced Carotid Ultrasonography and Serum Biomarkers of Inflammation and Atherosclerosis

**Presenter:** Linda Wang, Medical Student

**Research Interest:** Clinical Rheumatology and Clinical Immunology

**Mentors:** Kimberly Liang MD

**Funding Source:** K23

**Authors:** Linda Wang BA, Yaming Li MD, MS, Douglas Landsittel PhD, Suresh Mulukutla MD, Steven Reis MD, Marc Levesque MD, PhD, Donald Jones MS, Rachel Gartland MD, Jennifer Avolio MBA, RVT, Ali Shoushtari MD, Flordeliza Villanueva MD, Larry Moreland MD, Kimberly Liang MD

**Introduction:** Neovascularization of the vasa vasorum (VV) is a key early feature of vulnerable plaques. Inflammatory biomarkers, including those elevated in rheumatoid arthritis (RA), are associated with increased plaque vulnerability. RA-related factors may promote vulnerable plaque formation, leading to elevated CV risk. Microbubble contrast-enhanced ultrasound (CU) is a novel technique validated for quantifying VV neovascularization, which is not measured by traditional imaging. We use CU to compare aVVD between RA subjects and non-RA control subjects. We further examine association of aVVD with biomarkers of inflammation.

**Methods:** CU was performed along the common carotid arteries (CCA) bilaterally in 87 RA and 101 non-RA control subjects. Using Myocardial Contrast Echocardiography 2.9 software, aVVD was quantified as ratio of mean CCA adventitial to lumen videointensity. Biomarkers (nitrite, CD40L, E-selectin, MMP-9, ICAM-1, VCAM-1, MPO, CRP, and ESR levels) were measured. CV risk factors and biomarkers were compared between RA and control subjects using Wilcoxon rank-sum or chi-square tests. Association of aVVD with biomarkers and CV risk factors, stratified by case status, was examined using Pearson and Spearman correlation, respectively, and linear regression models adjusted for number of CV risk factors and age.

**Results:** RA subjects were older (59.6 ± 12.0 vs 56.1 ± 14.8 years; p = 0.01) with greater number of CV risk factors (40.2% vs 20.6% had 3 risk factors; p = 0.003) compared to controls. aVVD was higher in RA subjects (0.64 ± 0.14 vs 0.61 ± 0.15; p = 0.02). In RA subjects, MPO was lower (422.8 ± 516.4 vs 604.4 ± 455.1 ng/mL; p = 0.0002) and ESR was higher (21 ± 16 vs 16 ± 13 mm/hr; p = 0.01). The other biomarkers did not differ significantly between groups. aVVD was correlated with MPO (r = -0.33, p = 0.001) and CRP (r = 0.25, p = 0.02) in control subjects; associations remained significant after adjusting for number of CV risk factors and age. No significant correlations were found between aVVD and biomarkers in RA patients. Number of CV risk factors was not significantly correlated with aVVD in RA and controls.

**Conclusion:** Using the novel CU technique, we found that aVVD is significantly higher in RA compared to control subjects, suggesting CU may quantify increased plaque vulnerability in RA patients with subclinical atherosclerosis. The differences in correlation of aVVD with inflammatory biomarkers and traditional CV risk factors between RA and control subjects suggest RA-related differences in atherosclerotic progression.
82-A Poster: Fosfomycin for treatment of multidrug-resistant pathogens causing urinary tract infection; A real-world perspective

Presenter: Ahmed Babiker, Clinical Fellow

Research Interest: Epidemiology
Infectious Diseases

Mentors: Ryan Shields PharmD

Authors: Ahmed Babiker MBBS, Lloyd Clarke BS, Ryan Shields PharmD

Introduction: Urinary tract infections (UTI) are the most common infection associated with multidrug-resistant (MDR) pathogens. With limited treatment options, there has been an increasing interest in the efficacy of fosfomycin; however, real-world clinical data are limited. Our objective was to assess the outcomes of hospitalized patients with MDR UTIs treated with fosfomycin.

Methods: Retrospective review of patients with carbapenem resistant (CRE) or extended spectrum ß-Lactamase producing (ESBL) Enterobacteriaceae, or vancomycin resistant Enterococcus (VRE) UTIs who received =1 dose of fosfomycin. UTI was defined as a urine culture with =1000 CFU/ml among patients (pts) with dysuria, increased urinary frequency, suprapubic or flank pain or tenderness, fevers, or altered mental status without an alternative etiology. We defined cure as resolution of symptoms within 7 days without reoccurrence within 30 days. Microbiological failure was defined as a positive urine culture within 14 days.

Results: 47 patients with MDR UTIs were included (18 VRE, 15 CRE, 14 ESBL). The median age was 65 years (20 – 95), 81% were women, and the median Charlson Comorbidity index was 5 (0 – 19). 23% of patients were immunocompromised. The most common symptoms included fever (28%), increased urinary frequency (28%), and altered mental status (26%). 78% (37/47) of cases were classified as complicated UTIs. 64% of cases met current CDC/NHSN definitions of UTI, and 51% were considered healthcare-associated. Fosfomycin was prescribed as empiric and definitive therapy in 34% and 66% of patients. 17% of patients received >1 dose of fosfomycin. Clinical cure at 48 hours occurred in 87% of patients. 14-day clinical cure rate was 94%. Improvement in signs and symptoms was documented in 52% (23/44) and presumed following discharge in the remaining 48% (21/44) of patients. Microbiologic failures occurred in 15%; 57% of patients with microbiologic failures were asymptomatic. 11% (5/44) of patients had recurrence by same pathogen within 30 days. Overall clinical cure rate without relapse at day 30 was 83% (39/47); one death was attributed to CRE bacteremia and pneumonia 12 days after UTI treatment. One patient experienced nausea, but tolerated repeat dosing. Outcomes did not vary across pathogens or by the number of fosfomycin doses.

Conclusion: Across a range of MDR pathogens causing UTIs, Fosfomycin was well-tolerated and effective for hospitalized pts. Fosfomycin represents an attractive oral option to preserve alternative agents for systemic infections. Future studies are needed to evaluate the benefit of repeated dosing.

Presenter: Ahmed Babiker, Clinical Fellow

Research Interest: Epidemiology
Infectious Diseases

Mentors: Ryan Shields PharmD

Authors: Ahmed Babiker MBBS, Julie Paronish PharmD, Cornelius Clancy MD, Min-Hong Nguyen MD, Ryan Shields PharmD

Introduction: Carbapenem resistant organisms (CROs) are a global healthcare threat. Our objectives were to identify emerging trends in the epidemiology of CROs and to describe the outcomes of patients following isolation of CROs.

Methods: Microbiology data were collected from 2000-2017 for the most common Gram-negative pathogens. Carbapenem-resistance was defined uniformly across the study period despite changes to susceptibility breakpoints used clinically. Patient records were linked to electronic health record and Social Security Death Index databases.

Results: 94,888 isolates from 64,422 patients were identified. E.coli was most common (ECOL; 34%) followed by P. aeruginosa (PSAR; 27%), K. pneumoniae (KLPN; 19%), Enterobacter spp. (ENT; 12%), S. marcescens (SERM; 5%), and Acenitobacter spp. (ACAT;3%). 9,882 (10.4%) isolates from 4,038 patients were carbapenem-resistant. Between 2000-2017, rates of carbapenem-resistance increased from 6% to 11%; incidence rates increased from 0.81 cases/1000 patient days to 1.65. PSAR was the most common CRO each year accounting for 89% of CROs in 2000 and only 48% in 2017. Other pathogens emerged as second most common over time. By time-series linear-regression, annual rates of carbapenem-resistance increased for each pathogen (P<0.01). Carbapenem DDDs/1000 patient days increased from 6.52 to 35.08 (P<0.001) and correlated with rates of CROs (P<0.001;R2=0.8131). Among unique patients with CROs, 57% were male, mean age was 58 years, 18% were transplant recipients, and 5% had cystic fibrosis. At time of CRO isolation, 41% of patients were in ICU; culture sites were respiratory (53%), wound (21%), urine (17%), and blood (8%). 83% of cases were considered healthcare-associated. More than 1 CRO was isolated from 2% of patients. At hospital discharge, 17% of patients died, 32% were transferred to long-term care facilities, and 38% were discharged home. Median length of stay was 26 days. Overall 30- and 90-day mortality rates were 19% and 31%, respectively. By multivariate logistic-regression analysis, ICU residence (adjusted odds-ratio=3.63), severe liver disease (aOR=2.25), bacteremia (aOR=1.55), ACAT isolation (aOR=1.53), and age (aOR per year=1.03) were independent predictors of death. Over the study period, 30-day mortality rates decreased from 24% to 17% (P=0.003; R2=0.433); pathogen-specific mortality rates decreased for both PSAR (24% to 14%; P=0.009) and non-PSAR (43% to 29%; P=0.001).

Conclusion: CROs have emerged in waves at our center causing high rates of mortality. Among surviving patients, a high percentage have recurrent infections and are never discharged home. Overall mortality rates have decreased over time, likely owing to improved therapies. Factors associated with mortality can be incorporated into prediction models to evaluate individual mortality risk at time of presentation.
Poster: The use of Online Tools for Antimicrobial Resistance Prediction by Whole Genome Sequencing in MRSA and VRE

Presenter: Ahmed Babiker, Clinical Fellow

Research Interest: Epidemiology
Infectious Diseases

Mentors: Lee Harrison MD

Funding Source: RO1

Authors: Ahmed Babiker MBBS, Mustapha Mustapha PhD, Marissa Pacey BS, Kathleen Shutt MS, Chinelo Ezeonwuka BS, Sara Ohm MS, Vaugh Cooper PhD, Jane Marsh PhD, Yohei Doi MD, Lee Harrison MD

Introduction: The antimicrobial resistance (AMR) crisis represents a serious threat to public health and the healthcare economy, and has resulted in concentrated efforts to accelerate development of rapid molecular diagnostics for AMR. In combination with publicly-available web-based AMR databases, whole genome sequencing (WGS) offers the capacity for rapid detection of antibiotic resistance genes. Here we studied the concordance between WGS-based resistance prediction and phenotypic susceptibility testing results for methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin resistant Enterococcus (VRE) clinical isolates using publicly-available tools and databases.

Methods: Clinical isolates prospectively collected at the University of Pittsburgh Medical Center between December 2016 and December 2017 underwent WGS. Antibiotic resistance gene content was assessed from assembled genomes by BLASTn search of online databases. Concordance between WGS-predicted resistance profile and phenotypic susceptibility as well as sensitivity, specificity, positive and negative predictive values (NPV, PPV) were calculated for each antibiotic/organism combination, using the phenotypic results as the gold standard. Phenotypic susceptibility testing and WGS results were available for 108 and 100 MRSA and VRE isolates respectively.

Results: Of 1242 isolate/antibiotic combinations, overall concordance was 99.0% with a sensitivity, specificity, PPV, NPV of 98.4% (95% CI, 97.0-99.3%), 99.6% (95% CI, 98.7-100%), 99.5% (95% CI, 98.4-99.8%), 98.7% (95% CI, 97.5-99.3%), respectively. Additional identification of point mutations in housekeeping genes increased the concordance to 99.4% and the sensitivity to 99.3% (95% CI, 98.2-99.8%) and NPV to 99.4% (95% CI, 98.4-99.8%).

Conclusion: WGS can be used as a reliable predictor of phenotypic resistance for both MRSA and VRE using readily-available online tools.
Methods to Improve Allocation of HCV Related Resources

Presenter: Yosra Kandil, Undergraduate Student

Research Interest: Epidemiology
Infectious Diseases

Mentors: Mohamed Yassin MD

Authors: Yosra Kandil Undergraduate Student, Mohamed Yassin MD, Heather Dixon MS, Muaz Aijazi MD, Marie Tuft MS

Introduction: Hepatitis C treatment and prevention are essential to the wellbeing of the county and the financial health of the hospital system. The primary objective of this study was to determine the areas and demographics within Allegheny County with higher occurrences of Hepatitis C in order to effectively allocate funds.

Methods: Medical records for Hepatitis C testing across Allegheny County were analyzed by gender, age, zip code, and time of testing (prior to or after the Pennsylvania hepatitis C screening law).

Results: Within 1386 zip codes in Allegheny county, 5 zip codes have significantly higher rates of positive hepatitis C testing. While most of the zip codes yielded .01% of the positive testing in the county, these five zip codes, 15132, 15210, 15206, 15219, and 15221, yielded between 2.06% and 4.03%. When examining these five zip codes, the median household income was consistently below state average (15221 does not have information on household income but has below average house value). Unemployment percentages in four of the five zip codes (excluding 15206) were consistently above the state average as well as black race population percentages. In regards to the Pennsylvania hepatitis C screening law, which went into effect on September 18th 2016, the rate of positive results did not change when compared to testing results prior to the law going into effect. The proportion of positive testing between men and women, as well as the average age of positive testing were consistent with state and national rates.

Conclusion: Allocation of hepatitis C awareness and prevention resources should be balanced to reflect the needs of certain areas in the county. The five most hepatitis C ridden zip codes in the area all consistently have low average income and high unemployment, suggesting that impoverished areas should receive more attention in regards to prevention as well as those with higher underemployment. The hepatitis C screening law in Pennsylvania did not increase the yield for positive testing but should continue to be analyzed with data added from 2017 as well. This screening process may be draining on hospital resources, however due to the recent nature of the law's effectiveness, more exploration into this area is needed.
86-A Poster: Tobacco Smoking as Prognostic Indicator in Sickle Cell Disease: A Retrospective Analysis of Prospectively Collected Data

Presenter: Nityam Rathi, Medical Student

Research Interest: Epidemiology
Hematology/Oncology

Mentors: Gregory Kato MD

Funding Source: University of Pittsburgh THINK Fellowship

Authors: Nityam Rathi BS, Seyed Nouraie MD, Gregory Kato MD

Introduction: Sickle cell disease (SCD) is an inherited blood disorder characterized by abnormal sickle-shaped red blood cells. Sickling creates a higher tendency in red blood cells to aggregate and stick to vascular beds, making vascular beds a target organ in SCD. In preliminary screening for a current drug study of high vascular risk SCD patients (characterized by high blood pressure, high estimated pulmonary blood pressure, proteinuria, and early mortality) at UPMC, smokers anecdotally seemed overrepresented. To date, there has not been a broad-based SCD study of smoking and vascular disease outcomes. We hypothesized that smoking could be linked to four important health outcomes that characterize high vascular risk.

Methods: Relevant prospectively-collected data from the walk-PHASST multi-center clinical trial (ClinicalTrials.gov Identifier NCT00492531) were used for this analysis. 672 adult SCD patients were separated into three groups: current smokers, former smokers, and non-smokers. In each group, normal distribution for continuous variables were inspected using histograms with addition of a normalized smoothed curve and Shapiro-Wilks test. Parametric or nonparametric analyses were more used for data analysis. P-values were calculated using either ANOVA, or Chi-Squared tests. Additionally, a survival analysis for time to death by smoking status was performed using the Kaplan-Meier and log rank test. Analyses were performed in R and Stata.

Results: About 15% of adults with SCD were active smokers, and 67% have never smoked. In univariate analyses, age, gender, systolic blood pressure, tricuspid regurgitation velocity (TRV, as a noninvasive marker of pulmonary hypertension), and estimated Glomerular Filtration Rate (EGFR), and pack-years show significance or relevant trends. Patients who never smoked are significantly younger, more likely to be female, have a lower systolic blood pressure, and have greater estimated glomerular filtration rate. Upon adjustment for age and gender, current and former smokers had a slightly higher TRV. Despite a very limited duration of follow up, over 20 months the survival analysis shows a trend toward lower mortality in patients who have never smoked, although it is not statistically significant (P=0.37).

Conclusion: Sickle cell smoking status demonstrates statistically significant associations with indicators of hypertension, pulmonary hypertension and renal function; as well as a non-significant relationship to mortality during follow-up. However, neither causation nor detailed associations can be determined from this limited dataset. The results of this retrospective analysis are exploratory and hypothesis-generating, and they support a need for further investigation of the consequences of smoking upon SCD outcome.
**Poster: Self-management Support for Patients with Hypertension Using Online Videos and Automated, Bi-directional Text-Messaging**

**Presenter:** Matthew Allen, Medical Student

**Research Interest:** Health Services

**Cardiology**

**Mentors:** Matthew Muldoon MD

**Funding Source:** T32

**Authors:** Matthew Allen BA, Taya Irizarry PhD, Julian Einhorn BS, Brian Suffoletto MD, Lora Burke PhD, Thomas Kamarck PhD, Bruce Rollman MD, Matthew Muldoon MD

**Introduction:** Hypertension is a leading cause of heart disease, stroke and kidney failure yet the US control rate is approximately 50%. Home blood pressure monitoring (HBPM) has been shown in clinical trials to lower BP but its mechanism(s) of effect are unknown and no patient-centered programs facilitating HBPM are in widespread use. The current pilot project sought a) to develop a convenient aide for patients attempting HBPM, and b) to explore putative behavioral mechanisms potentially linking HBPM with BP changes.

**Methods:** We recruited 43 patients from three clinical sites (an urban emergency department, a primary care clinic, and a hypertension specialty center). Basic hypertension knowledge was delivered at enrollment via online videos. An automated, bidirectional text-message system sent prompts instructing the participant to measure and text back their BP at 4 self-selected times per week for 6 weeks. Participants received rolling average BP feedback with each submission and summary reports at the end of each 2-week period. An exit interview was conducted with all willing participants (n=40) at the end of the study period.

**Results:** Median adherence to MyBP prompts over six weeks was 79% (72% Emergency Department, 84% Primary Care and 96% Hypertension Center, H[2]=5.56, p=0.06). Adherence did not vary by age, gender, race, education or baseline use of texting. Exit interview data revealed that the large majority of participants viewed the program very positively and favored longer term participation. The majority of participants reported making at least one healthy behavior change relating to diet, exercise, stress-reduction, or medication adherence. Qualitative analysis of the exit interviews identified three primary themes as contributing most to patients’ decision to initiate a behavior change: 1) increased hypertension literacy attributed to educational videos presented at enrollment, 2) increased day-to-day salience of blood pressure levels as a result of consistent HBPM, and 3) use of BP readings as feedback, with high readings triggering intrinsic motivations to make behavior changes.

**Conclusion:** Automated programs facilitating HBPM are acceptable and useful to an inclusive and diverse sample of patients with hypertension and, further, that consistent HBPM can encourage improvements in health behaviors and hypertension self-management.
**Poster Abstracts**

88-A  **Poster**: Association of state laws mandating prescription drug monitoring program use by prescribers on discontinuation of chronic opioid therapy in Veterans

**Presenter**: Jonathan Arnold, Post-Doctoral Fellow

**Research Interest**: Health Services

General Internal Medicine

**Mentors**: Walid Gellad MD MPH

**Funding Source**: T32, VA

**Authors**: Jonathan Arnold MD MSE, Xinhua Zhao PhD, Florentina Sileanu MS, Maria K. Mor PhD, John P. Cashy PhD, Patience Moyo PhD, Carolyn T. Thorpe PhD MPH, Chester Good MD MPH, Thomas R. Radomski MD MS, Michael J. Fine MD MSc, Walid F. Gellad MD MPH

**Introduction**: Several states have mandated that prescribers check prescription drug monitoring programs (PDMPs) prior to opioid prescribing and periodically during therapy. Despite concerns about inappropriately-abrupt opioid discontinuation resulting from this policy, no studies have evaluated the extent to which this occurs. Our objective was to evaluate the impact of PDMP mandates on discontinuation of chronic opioid prescribing for Veterans managed in the Veterans Affairs Administration (VA) Healthcare System.

**Methods**: We conducted an interrupted time-series (ITS) study of opioid discontinuation in Veterans without cancer in states that implemented a PDMP use-mandate from 2010-2014: Ohio (OH; Nov 2011), West Virginia (WV; Jun 2013), Kentucky (KY; Jul 2012), and Tennessee (TN; Apr 2013). We used Veterans in neighboring states without a mandate as controls. We built monthly cohorts of Veterans with ≥305-days of a VA-prescribed opioid in the prior 365-days. We defined discontinuation as a 90-day period without a VA-prescribed opioid. For each state with a PMDP-mandate and its pooled control we estimated monthly discontinuation rates, adjusted for patient-level demographic and clinical covariates. We calculated the difference between the mandate-states and their controls; we used these differences in our ITS models with offset and slope-change terms at the time of the mandate. We included 12-months prior-to and following the mandate in each state. All reported percentages represent absolute percentage points.

**Results**: We built monthly cohorts for 4 PMDP-mandate and 12 neighboring control states (3-7 controls for each mandate state). Monthly cohort sizes ranged from 4,733-8,909 Veterans in the mandate states and 11,985-41,163 in the controls, a total of 2.5M veteran-months. The average adjusted discontinuation rates in the 12 months prior to (after) the mandates were 0.7 (0.9)% in OH, 0.7 (0.7)% in WV, 0.8 (1.3)% in KY, and 0.8 (0.9)% in TN. There was no difference in the pre-mandate discontinuation rate between mandate states and controls. TN was the only state with an increasing baseline discontinuation trend of 0.02%/month (p=0.03) compared to its control. KY’s mandate was associated with an immediate 1.03% (p<0.001) increase in discontinuation rate. KY’s and TN’s mandates were associated with a decreasing discontinuation trend of -0.09% (p<0.001) and -0.05% (p<0.001) per month respectively. OH’s and WV’s mandates had no associated change.

**Conclusion**: For VA-managed Veterans, state laws mandating prescriber PDMP use had little absolute effect on discontinuation of chronic opioid prescribing. We did observe a clinically significant but short lived increase in opioid discontinuation in KY immediately following its mandate, however the overall discontinuation rate remained low. These results suggest that PDMP use mandates did not cause abrupt discontinuation of long-term opioid therapy within VA.
90-A  **Poster:** Transplant Clinical and Financial Outcomes as a Function of Transplant Care Venue: VA, non-VA, and Dual-Use

**Presenter:** Winn Cashion, Clinical Fellow

**Research Interest:** Health Services
Renal-Electrolyte

**Mentors:** Steve Weisbord MD

**Funding Source:** Dept Veterans Affairs

**Authors:** Winn Cashion MD, Steve Weisbord MD, Walid Gellad MD, Michael Fine MD, Florentina Sileanu MSc, Maria Mor PhD, Virginia Hale , Jennifer Hale BS

**Introduction:** Prior research demonstrates that many Veterans eligible for care within the VA Healthcare System are simultaneously Medicare enrollees. Consequently, many Veterans receive some care at the VA and some care from non-VA providers. Prior work demonstrates that for certain medical conditions, such “dual-use” Veterans have increased medical costs and are at higher risk for poor health outcomes relative to Veterans receiving all their care through the VA. Organ transplantation represents the definitive treatment for many otherwise incurable diseases. Veterans dually enrolled in the VA and Medicare can undergo kidney transplantation and receive post-transplant care at seven national VA transplant centers, at non-VA institutions, or both depending on their proximity to the VA and personal preference. As such, our objective is to assess the relative clinical outcomes and healthcare-related costs among Veterans with kidney transplants eligible for both VA care and Medicare [dual eligible] based on post-transplant care setting [VA, non-VA, or both].

**Methods:** RESEARCH DATA: We will construct a cohort of Veterans eligible for care within the VA and through Medicare who have a history of kidney transplant based on procedure and/or diagnostic codes. We will link this cohort with the Center for Medicare Services’ [CMS] inpatient and outpatient claims dataset and the VA's Corporate Data Warehouse that contains inpatient, outpatient, lab testing, and pharmacy data. We will obtain transplant-related healthcare costs from the CMS MedPAR file and VA reimbursement documentation.

EXPOSURE OF INTEREST: Whether the Veteran’s kidney transplantation and post-operative care occurred exclusively at the VA, exclusively outside the VA, or dual-use care [both within and outside the VA].

OUTCOMES OF INTEREST: Clinical outcomes include allograft rejection, all-cause mortality, and all-cause hospitalizations. Financial outcomes include overall post-transplant and transplant-specific healthcare costs.

ANALYTIC METHODS: We will use descriptive statistics to characterize Veteran kidney transplant epidemiology. We will examine clinical outcomes using Cox proportional hazards and Poisson models. Healthcare costs will be assessed with linear regression, adjusting for underlying comorbidities and demographics.

**Results:** We are currently in the process of generating the transplant cohort from VA and Medicare data. To date, we have identified over 7,000 such Veterans.

**Conclusion:** By characterizing Veteran kidney transplant epidemiology and elucidating health and economic outcomes based on care venue, we anticipate that this project's findings will inform funders, providers, and Veteran patients of the comparative efficacy and costs of VA and non-VA transplant care.
Introduction: Oral anticoagulation (OAC) is associated with stroke risk reduction in patients with atrial fibrillation (AF). Black individuals and women with AF have higher stroke rates, these disparities largely due to lower use and efficacy of traditional warfarin-based OAC in these groups. Less is known about race/ethnicity and sex-related differences in novel direct-acting oral anticoagulant (DOAC) use in patients with AF. Our aim was to compare OAC and DOAC initiation by sex, race, and ethnicity in a real-world, national cohort of patients with AF.

Methods: We used claims data from a 5% sample of Medicare beneficiaries to identify patients with newly-diagnosed AF between 2013-2014. We excluded those without continuous Medicare enrollment. The primary outcome was the initiation of any OAC (warfarin and DOAC - apixaban, dabigatran, rivaroxaban) after AF diagnosis based on prescription fill data. Among OAC initiators, we compared DOAC vs. warfarin use. We used logistic regression to assess the association between sex, race/ethnicity (white, black, Hispanic) and OAC initiation, adjusting for sociodemographic factors, comorbidities, and stroke risk (CHA2DS2-VASc score).

Results: The cohort of 47,952 patients with AF included 17,935 women, 3282 blacks, and 1958 Hispanics. Overall OAC initiation was low (49.2% whites, 48.1% blacks, and 47.5% Hispanics). After adjusting, blacks (odds ratio (OR) 0.84; 95% CI, 0.78-0.91) and Hispanics (OR 0.90; 95% CI, 0.82-0.99) were less likely than whites to initiate any OAC. Women were less likely than men to initiate any OAC, OR 0.59 (95% CI 0.55-0.64). Among OAC initiators, DOAC use was low (35.8% whites, 29.3% blacks, and 40.0% Hispanics). After adjusting, blacks were less likely to initiate DOACs than whites, OR 0.80 (95% CI 0.71-0.90); the odds of DOAC initiation did not differ for Hispanic and white patients; OR 1.10 (95% CI 0.95-1.27). There was no gender difference in DOAC use among OAC initiators, OR 0.98 (95% CI 0.88-1.10).

Conclusion: In a national cohort of Medicare beneficiaries with newly diagnosed AF, OAC initiation was lower in blacks, Hispanics, and women. Among OAC initiators, blacks were less likely to initiate DOACs, with no differences identified by Hispanic ethnicity or gender. These findings, in a real-world cohort of medically insured patients, show that blacks with AF were less likely to receive novel DOACs - easier to use, potentially safer, and more effective than warfarin in stroke prevention. Identifying modifiable causes of treatment disparities is needed to improve the quality of care for all patients with AF.
**Poster Abstracts**

**92-A Poster:** Racial and Ethnic Differences in the Medical Treatment of Opioid Use Disorders within the VA Healthcare System Following Non-Fatal Opioid Overdose

**Presenter:** Utibe Essien, Junior Faculty

**Research Interest:** Health Services
General Internal Medicine

**Mentors:** Walid Gellad MD

**Funding Source:** VA

**Authors:** Utibe Essien MD, Florentina Sileanu, Jane Liebschutz MD, Chester Good MD, Xinhua Zhao PhD, Maria Mor PhD, Michael Fine MD, Walid Gellad MD

**Introduction:** There has been slow adoption of medication-assisted treatment (MAT) in the US, despite substantial morbidity and mortality from opioid misuse and overdose. Even after non-fatal opioid overdose, research shows that few enter addiction treatment, and opioid prescribing patterns frequently are unchanged. Little is known about race/ethnicity differences in care after non-fatal overdose, despite known disparities in opioid prescribing. Our aim was to assess the association of race and ethnicity on receipt of MAT and prescription opioids before and after a non-fatal overdose in a national cohort of patients from the Veterans Health Administration (VA).

**Methods:** Using data from the VA Corporate Data Warehouse and Pharmacy Benefits Management Services, we identified all Veterans enrolled in VA from 2011-2013 who had a hospitalization or emergency room visit for non-fatal opioid overdose based on established ICD-9 codes. We excluded patients in hospice care, those with missing or "other" race/ethnicity, and those who died within 7 days of the overdose date. We categorized race/ethnicity as white, black, or Hispanic. Our primary outcomes were: 1) MAT prescription (buprenorphine, naltrexone) or =1 methadone clinic visit within 30 days after overdose, and 2) change in opioid prescription fills within 30 days after overdose from the 30 days before. We used logistic regression, adjusting for age, to test whether MAT receipt after overdose differed by race/ethnicity and used difference-in-differences analyses to test whether change in opioid prescribing after overdose differed by race/ethnicity.

**Results:** Among 5746 Veterans with a non-fatal overdose, 14.3% were black, 4.2% were Hispanic, and 7.5% women; mean age (SD) was 60.2 (13.7) years. After overdose, 3.3% of Veterans received any MAT, with no difference observed comparing black Veterans to white, adjusted odds ratio (aOR) 1.32, 95% CI 0.90,1.92. Hispanic Veterans were more likely than whites to receive MAT after overdose (aOR 1.87, 95% CI 1.04, 3.37).Before overdose, opioid prescriptions varied by race/ethnicity (65.8% of white Veterans, 59.6% black and 62.9% Hispanic, p value <0.01). After overdose, prescription opioid use decreased significantly to 49.3% in whites (-16.5% absolute difference), 44.5% in blacks (-15.5% absolute difference), and 46.4% in Hispanics (15.9% absolute difference). These decreases in opioid prescription after overdose did not differ between groups (overall p-value 0.88).

**Conclusion:** In a national cohort of Veterans with a non-fatal opioid overdose, overall MAT receipt was low with slightly higher rates among Hispanic Veterans compared to whites. After overdose, opioid prescribing decreased across all groups with no difference observed by race/ethnicity. Further examination of racial and ethnic disparities in post-overdose care in contemporary and other real-world patient cohorts is vital to improve quality of care for all patients.
93-A  **Poster:** Nephrology Population Health Management and E-consults: Specialty assistance without the Office Visit

**Presenter:** Manisha Jhamb, Junior Faculty

**Research Interest:** Health Services  
Renal-Electrolyte

**Funding Source:** Seed funds

**Authors:** Manisha Jhamb MD, Khaled Abdel-Kader MD

**Introduction:** Over 30 million US adults have chronic kidney disease (CKD), leading to substantial morbidity, mortality and health care costs. Given the growing CKD population, the relative shortage of nephrologists, and fragmented care, there is a need to improve access to nephrology expertise in an efficient manner. The goal of this pilot study was to test the usability and acceptability of electronic health record (EHR)-based CKD population health management (PHM).

**Methods:** This pilot study was conducted in 2 primary care physician (PCP) practices at the University of Pittsburgh Medical Center and all PCPs from both practices were enrolled. We developed an EHR CKD registry in Epic that identified all patients with an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m2 based on creatinine in prior 12 months. We developed a PHM dashboard that leveraged the CKD registry to aggregate data and efficiently analyze it. The dashboard included validated risk prediction models for estimating the probability of kidney failure as well as longitudinal tracking of kidney function, electrolytes, and blood pressure. We identified CKD patients who were in the highest risk decile of the population for developing kidney failure in 5 years and who were not receiving nephrology care. Thereafter, PCPs were offered an electronic consultation (e-consult) or a traditional office consultation. If an e-consult was chosen, a nephrologist reviewed the patient’s chart and provided concise, actionable recommendations to the PCP. The intervention was refined to harmonize with PCP workflow. Additionally, we conducted an anonymous, web based survey of PCPs from the pilot practices to determine the intervention’s acceptability.

**Results:** From January to December 2016, we offered the intervention to 46 patients, and provided services to 37, indicating outstanding PCP acceptance (~90%). Among the 37 patients (mean age 69 yrs, 30% females, eGFR 33ml/min), the median 5-year risk of ESRD was 8.5% and 38% had uncontrolled hypertension. Recommended changes to patient treatment included hypertensive regimen intensification in 43%, renin angiotensin aldosterone blocker in 27%, and at least 1 change to patient pharmacotherapy in 61% of the patients. Among the 9 PCP's who completed the survey, 89% believed the recommendations were timely and useful and 100% would recommend the intervention to a colleague.

**Conclusion:** EHR-based population health management can identify high risk CKD patients, and facilitate timely communication, collaboration, and the provision of evidence based recommendations between nephrologists and PCPs.
94-A  Poster: Factors Associated with Long-Term Retention in Buprenorphine Based Addiction Treatment Programs

Presenter: Amy Kennedy, Post-Doctoral Fellow

Research Interest: Health Services
General Internal Medicine

Mentors: Jane Liebschutz MD

Funding Source: T32

Authors: Amy Kennedy MD, Jessica Merlin MD, Charles Wessel, Rebecca Levine MD, Kendall Downer MD, Iman Hassan MD, Megan Raymond BS, Deborah Osakue, Jane Liebschutz MD

Introduction: The average length of opioid agonist therapy with buprenorphine (BUP) for opioid use disorder is less than 6 months. We conducted a systematic review to determine what treatment level factors (dose, treatment setting and behavioral therapies) were associated with longer retention in BUP treatment.

Methods: We searched Medline, Embase and the Cochrane Database of Systematic Reviews in February 2018. Articles were restricted to randomized-controlled trials on human subjects, written in English, and contained >24 weeks of objective data on retention in BUP treatment. We assessed whether dose of BUP, treatment setting, or co-administration of behavioral therapy were associated with retention rates.

Results: Over 14,000 articles were identified. Twenty-two articles met final inclusion criteria, describing a total of 13 studies (Figure 1). There was significant heterogeneity in measurement of retention. Measures included days in treatment (n=10), urine drug testing for BUP (n=2), and a combination of days in treatment and plasma level testing for BUP (n=1). Three studies compared doses of BUP between 1-8mg and showed significantly higher rates of retention with higher doses (p-values <0.01). All other studies in our review utilized maintenance BUP doses between 8mg-24mg daily. No study found a significant difference in retention between BUP alone and BUP plus behavioral therapy (p-values > 0.05). Starting BUP prior to initiation in outpatient treatment programs (inpatient induction or within criminal justice settings) was significantly associated with retention in BUP treatment (p-values 0.009 and 0.005 respectively).

Conclusion: Setting of treatment initiation and higher BUP dose are associated with improved long-term treatment retention. More data on BUP treatment programs is needed as well as a standardized approach to defining retention in BUP treatment programs.
95-A **Poster:** Provider Perspectives on Barriers and Facilitators of Long-Acting Reversible Contraceptive Use at UPMC

**Presenter:** Anna Leone, Medical Student

**Research Interest:** Health Services
- General Internal Medicine

**Mentors:** Natasha Parekh MD

**Funding Source:** UPMC Center for High-Value Health Care

**Authors:** Anna Leone BA, Kelly Williams MPH, Elizabeth Swart BA, Sonya Borrero MD, Natasha Parekh MD

**Introduction:** In August 2012, the Affordable Care Act’s contraceptive mandate required insurance plans fully cover at least one contraceptive method type from each of 18 FDA-approved method categories. Though a primary goal of the mandate was to eliminate cost as a barrier to accessing the full range of contraceptive methods including long-acting reversible contraception (LARC) (i.e., intrauterine devices and implants), only 12% of women in the United States utilized LARC methods in 2014. Qualitative interviews were conducted with obstetrics/gynecology (OB/GYN) providers in UPMC, with nationally comparable rates of LARC usage, to understand practice- and system-based barriers and facilitators to LARC access.

**Methods:** We conducted semi-structured interviews with OB/GYN providers who inserted at least three LARCs in 2017. Using claims data, we compiled a list of 107 eligible providers and conducted a total of 30 total interviews. Providers were defined as “high-uptake” if they administered more than 42 LARCs in 2017 (the median) and “low-uptake” if they administered less than 42 LARCs in 2017. Interviews were recorded and transcribed verbatim. Two coders developed a codebook based on an iterative review of transcripts and then applied themes to remaining transcripts, holding regular meetings to adjudicate coding disagreements. Directed content analysis was utilized throughout the analytic process. Our study population included 15 “high-uptake” providers and 15 “low-uptake” providers, representing 28 obstetricians/gynecologists and two nurse practitioners. Providers placed 68 LARCS in 2017 on average, practiced for 15.5 years on average, and 76% were women.

**Results:** Preliminary themes focused primarily on practice-level barriers and facilitators, as well as one system-level barrier. Providers described several practice-level barriers to LARC access, including, (1) policies requiring women to return for a second appointment to complete LARC insertion; and (2) policies requiring women to return while menstruating to complete LARC insertion. Providers mentioned practice-level facilitators to LARC access, including, (1) availability of ancillary clinical staff; and (2) patient education materials. Time in provider schedules and practice stocking of the LARC method were mentioned as both facilitators and challenges to LARC access, and both were practice-dependent rather than standardized across all offices represented in the sample. Requiring insurance pre-authorization prior to insertion was commonly described as a system-based barrier to LARC access.

**Conclusion:** Patient access to LARC methods can be complicated by clinic-level barriers that are heavily practice-dependent, in addition to system-level barriers. Understanding the diversity of practice-based barriers and developing a plan to address challenges are vital to optimize LARC access.
**Poster: **Physician Satisfaction with Health Plans: Results from a National Survey

**Presenter:** Natasha Parekh, Junior Faculty

**Research Interest:** Health Services
General Internal Medicine

**Mentors:** William Shrank MD MSHS

**Authors:** Natasha Parekh MD MS, Sheryl Savage, Amy Helwig MD MS, Patrick Alger, Ilinca Metes BS, Sandra McAnallen MA BSN, William Shrank MD MSHS

**Introduction:** Physician satisfaction is associated with patient satisfaction, adherence to treatment recommendations, and quality. However, burnout is prevalent, and physician experience with health plans is likely a key contributor. Our existing knowledge of physician satisfaction with health plans, however, is limited, mixed and outdated. We therefore explored physician satisfaction with health plans, and assessed which physician and plan characteristics are associated with greater satisfaction.

**Methods:** We conducted a cross-sectional analysis of de-identified physician satisfaction surveys for US health plans in 2016. We included the following satisfaction domains as outcomes of interest: overall health plan rating; financial issues; utilization and quality management; network/coordination of care; pharmacy issues; call center experience; provider relations; and recommendation of the sponsor plan to other physicians' practices. We assessed the association between the following characteristics and outcomes of interest using multivariable linear regression, weighted by the number of respondents: vertical (payer-provider) integration status, health plan size, practice size, provider type, and years of practice.

**Results:** We analyzed surveys from 3,158 physicians on 74 health plans. We observed highest satisfaction in overall plan rating, finance, and call center domains (adjusted means 3.25), and lowest satisfaction in pharmacy (adjusted mean 3.02). The largest and smallest plans and vertically integrated plans had the highest satisfaction: 76% of physicians recommended vertically integrated plans while 66% of physicians recommended non-vertically integrated plans to others (p<0.001). Solo practitioners rated overall plan rating, finance, utilization/quality management and pharmacy domains more favorably than physicians in larger practices (p<0.001), while primary care physicians rated overall plan rating, finance, and utilization/quality management more favorably than specialists (p<0.001).

**Conclusion:** Our findings demonstrate that there is significant opportunity to improve physician satisfaction with health plans in all satisfaction domains, especially in pharmacy/formulary management. Since provider satisfaction is becoming increasingly recognized as a critical outcome, our findings suggest that health plans have a unique and important opportunity to improve physician satisfaction and highlight potential interventions such as prioritizing provider relationships, optimizing formulary management, reducing administrative burden, and providing resource support. Additionally, interventions could specifically target physicians in larger practices and non-vertically integrated and mid-size health plans. As physicians are required to adapt to a rapidly transforming healthcare landscape, it will be imperative for health plans to prioritize physician satisfaction moving forward.
97-A  **Poster:** The Impact of Medicare Star Rating Adherence Measures on Medication Adherence for Targeted and Non-Targeted Medications

**Presenter:** Natasha Parekh, Junior Faculty

**Research Interest:** Health Services  
General Internal Medicine

**Mentors:** William Shrank MD MSHS

**Funding Source:** Express Scripts

**Authors:** Natasha Parekh MD, Kiraat Munshi PhD, Inmaculada Hernandez PharmD, Walid Gellad MD, Rochelle Henderson PhD, William Shrank MD MSHS

**Introduction:** In 2012, Medicare incorporated medication adherence for oral antidiabetics, renin-angiotensin system (RAS) antagonists, and statins as highly weighted measures in star rating calculations. In the same year, health plans began receiving Quality Bonus Payments for achieving higher star ratings. It is unclear how these policy changes affected adherence to medications targeted by these policies and whether any impact spilled over to other chronic disease medications.

**Methods:** We performed quasi-experimental interrupted time series analyses with multivariable segmented linear regression models to assess monthly changes in medication adherence (as measured by proportion of days covered) over a seven-year period from 2010 to 2016 using Medicare administrative claims data from a large pharmacy benefits manager. We conducted two separate sets of analyses: the first examined whether policy changes affected medication adherence for the 3 targeted therapy classes, and the second assessed the association between policy changes and adherence to five chronic disease therapy classes not considered in star ratings calculations (thiazides, beta blockers, calcium channel blockers, non-statin anti-hyperlipidemics, and levothyroxine). For the second analysis, we further compared adherence between beneficiaries who concomitantly used and did not use star rating medications.

**Results:** We studied 240,811 Medicare beneficiaries on oral antidiabetics, 500,958 on RAS antagonists, 471,135 on statins, 464,910 on beta blockers, 392,762 on thiazides, 397,359 on calcium channel blockers, 165,151 on non-statin anti-hyperlipidemics, and 323,803 on levothyroxine. There was a significant increase in monthly adherence for all star rating and non-star rating medications after 2012 (p<0.001). Adherence for oral antidiabetics, RAS antagonists, and statins was 11.2%, 8.1%, and 3.7% higher than it would have been in the absence of star ratings policy changes, respectively (p<0.001). Changes in adherence for non-star rating anti-hypertensives and anti-hyperlipidemics were higher among those concomitantly on star ratings medications compared with those who were not (p<0.001). Levothyroxine adherence trends did not significantly differ between those using and not using star rating drugs.

**Conclusion:** Incentivizing medication adherence in the star rating program was effective in increasing adherence to medications targeted by the policy change and also non-targeted medications that treat the same diseases. As policymakers seek to determine the optimal number and type of quality measures for improving healthcare delivery without increasing administrative burden, it is important to consider that incentives not only can improve performance of targeted measures, but can also spill over to promote improved performance in related outcomes. Our findings can ultimately inform future approaches to quality measure development and implementation.
**Introduction:** In 2014, health insurance marketplaces were implemented under the Affordable Care Act (ACA). Pennsylvania additionally expanded Medicaid under the ACA in 2015. By March 2017, 716,000 new Pennsylvanians enrolled in Medicaid. To date, 370,000 have purchased a marketplace plan. The ACA and Medicaid expansion have improved rates of cancer screening nationwide (Zhao G, et al. Am J Prev Med 2018.). Data on the ACA’s impact on direct cancer care is limited. We aim to determine how the ACA and Medicaid expansion have impacted breast cancer care in Pennsylvania.

**Methods:** The Pennsylvania Cancer Registry was queried for women aged 20-75 diagnosed with breast cancer from 2010-2015. Demographic, tumor, and treatment characteristics were evaluated for each case. The primary group of interest, women aged 20-64, was compared to the control group of women aged 65-75, who were Medicare-eligible and unlikely to be impacted by ACA provisions. Diagnosis stage was assessed using the AJCC 7th Edition. Guideline-concordant treatment endpoints were constructed using American College of Surgeons and National Comprehensive Cancer Network guidelines. Diagnosis and treatment endpoints were compared for the years 2010-2013 and 2014-2015 (pre- and post-ACA).

**Results:** The proportion of stage I-II breast cancers among women aged 50-64 increased from 80.9% to 82.9% (p=0.0025) following ACA implementation. Stage III breast cancers decreased from 11.3% to 9.8% (p=0.0001), and the rate of diagnosis of metastatic disease was unchanged. Stage of diagnosis did not change following ACA implementation for women aged 65-75. Guideline-concordant adjuvant radiation following breast-conserving surgery and perioperative chemotherapy were administered at high rates (> 95%) for all women and were unchanged post-ACA. Guideline-concordant adjuvant hormonal therapy was administered more frequently following ACA implementation for both women aged 20-64 (77.40% v. 84.17%, p<0.0001) and 65-75 (78.26% v. 86.18%, p<0.0001), but this trend began before 2014.

**Conclusion:** ACA implementation and Medicaid expansion in Pennsylvania was associated with an increased proportion of stage I-II breast cancers and commensurate decrease in stage III diagnoses for women aged 50-64, but stage of diagnosis for women aged 65-75 was unaffected. This suggests that increased insurance coverage contributed to earlier stage of diagnosis of breast cancer in Medicare-ineligible women, likely via increased screening mammography. Administration of perioperative chemotherapy and adjuvant radiation therapy following breast-conserving surgery was unchanged by ACA implementation. Adjuvant hormonal therapy increased among women in all age groups examined after ACA implementation, suggesting that this increase was likely the result of other practice changes.
99-A  **Poster:** Don’t Just Do Something, Sit There! Assessing the Impact of Sitting at the Bedside on Patients’ Satisfaction with their Doctors

**Presenter:** Anna Donovan, Junior Faculty

**Research Interest:** Medical Education
General Internal Medicine

**Mentors:** Jennifer Corbelli MD

**Funding Source:** Beckwith Foundation Frontline Innovation Project

**Authors:** Anna Donovan MD, Carla Spagnoletti MD, Scott Rothenberger PhD, Raquel Forsythe MD, Jennifer Corbelli MD

**Introduction:** Improving patient satisfaction remains an important yet elusive endeavor for academic medical centers. One study demonstrated that hospitalist attending physicians in a non-teaching hospital had higher-rated communication skills when sitting compared to standing at the bedside during rounds. It is unclear whether these data can be applied to resident-led multidisciplinary team rounds, during which 7-8 providers round together. We hypothesized that if resident team leaders sat during morning rounds that patient satisfaction would improve without impacting rounding efficiency.

**Methods:** We performed a cluster-randomized trial with crossover in which internal medicine (IM) and surgery residents served as their own controls. Each resident team leader (IM N=18; Surgery N=8) was assigned to sit or stand on a chair at the bedside during alternating weeks in May and June of 2018. Research assistants administered electronic surveys to 5 randomly selected patients per team per week for the study period of 8 weeks. In addition, all IM interns and residents (N=54) from participating teams were invited to complete a post-rotation survey about their perceptions of sitting vs. standing during rounds.

**Results:** A total of 18 IM and 8 surgery resident team leaders participated. Surveys were collected from 583 patients. There was no statistically significant difference in patient perception of physician skill in giving complete information, using plain language, showing interest in patients and their problems, or giving patients time to ask questions (all p>0.05). Results from IM and surgery did not differ. Surveyed IM residents (response rate 80%) felt that rounding duration did not differ. Most indicated that sitting at the bedside was already their standard practice.

**Conclusion:** When randomizing medicine and surgery residents to sit or stand during team rounds, we found no difference in patient perceptions of physician communication. While sitting positively impacted attending hospitalists’ patient-rated communication skills when rounding alone, this was not replicated with resident-led team rounds. We suspect that one member sitting, while all others stand, is not sufficient to impact the patients’ perception of the entire encounter. Further, patients rated resident communication highly in both groups, so a ceiling effect may have prevented us from detecting any difference. We speculate that sitting during one-on-one patient encounters (e.g. initial history-taking, breaking bad news), rather than team-based encounters, may have greater impact in teaching hospitals. Standing was non-inferior to sitting during rounds. Our results suggest that initiatives to optimize patient communication and satisfaction in teaching hospitals should be focused elsewhere. References: 1. Merel et al, JHM, 2016.
Poster: SGIM Leadership in Health Policy Curriculum Initiative

Presenter: Molly Fisher, Clinical Fellow

Research Interest: Medical Education
General Internal Medicine

Mentors: Melissa McNeil MD

Funding Source: Department of General Internal Medicine

Authors: Molly Fisher MD, Sarah Candler MD, Susan Lane MD, Colin Robinson MD, Latonya Riddle-Jones MD, Michi Yukawa MD

Introduction: Several major healthcare organizations have stated the importance of educating physicians on health policy. However, there are no current guidelines on what information should be taught to physicians or trainees, and how this content should be delivered. Based on a Delphi survey of health policy experts conducted by the authors, four major topics were identified as essential components of a health policy curriculum for internal medicine residents: Medicare, Medicaid, social determinants of health, and private insurance and the healthcare marketplace.

Methods: Members of the Society for General Internal Medicine (SGIM) Leadership in Health Policy (LEAHP) fellowship worked to create a standardized health policy curriculum. The curriculum involves four separate one-hour lessons that can be taught independently or as a complete package in either small or large group settings. Each lesson consists of a didactic component and a group activity. The authors of this curriculum plan to pilot the curriculum at their home institutions during the 2019-2020 academic year. Once the pilot year is complete, a standardized evaluation tool that assesses attitudes and knowledge will help to inform the authors on how to alter the curriculum prior to dissemination.

Results: As this project is still in the pilot stages, we do not currently have results. The results will include a pre-survey and post-survey that assess the residents’ knowledge and attitudes of the material presented in the curriculum.

Conclusion: Creating this curriculum has been a large multi-institutional effort with faculty members from a wide variety of backgrounds. The hope is that the final product will be publicly available and allow institutions without health policy expertise to teach this information to their residents.
**101-A Poster: Increasing Health Profession Students’ Interprofessional Competencies: The Interprofessional Dedicated Education Unit (IPDEU)**

**Presenter:** Rachel Jantea, Post-Doctoral Scholar

**Research Interest:** Medical Education

Geriatric Medicine

**Mentors:** Rollin Wright MD

**Funding Source:** T32

**Authors:** Rachel Jantea MD, Victoria Hornyak DPT, GCS, Cassandra Leighton PhD, Teresa Pacella LSW, Rosemary Hoffman PhD, RN, Sandra Engberg PhD, RN, CRNP, Subashan Perera PhD, Susan Meyer PhD, Benjamin Reynolds MSPAS, PA-C, Debra Weiner MD, David Michael Elnicki MD, Alton Everette James JD, MBA, Rollin Wright MD

**Introduction:** Health professionals work in interprofessional (IP) teams to care for older adults. Interprofessional education (IPE) is now required for health profession students, but the best educational model is unknown. Further, clinical preceptors are often untrained in IPE, creating heterogeneity in students’ IPE experiences. To address these needs, we designed and evaluated an Interprofessional Dedicated Education Unit (IPDEU) acute care IPE experience for health profession students.

**Methods:** We designated the 5G neurotrauma unit at UPMC Presbyterian Hospital the IPDEU. Unit nurse, occupational therapy (OT), physical therapy (PT), and speech therapy (ST) providers were trained as IPE instructors in summer 2018. Instructor training utilized web-based skill modules (2 hours) and live simulation scenarios (4 hours) to teach IP practice skills and IPE-specific instructor skills. Learners were University of Pittsburgh health profession students (3 audiology, 13 nursing, 8 OT, 9 PT, 9 ST, 8 physician assistant) rotating on the IPDEU in fall 2018. Pairs of students (from different health professions) each spent 2 half-day sessions on the IPDEU within a one-week period (one each with a nurse IPE instructor & a therapy IPE instructor). During IPDEU sessions, students actively observed IPE instructors during usual patient care activities. Instructors facilitated active observation of IP aspects of care specifically (not clinical skills) using skills like asking IPE-directed questions and thinking-out-loud. A group debrief concluded each session. Students self-rated their IP competencies using the Interprofessional Collaborative Competency Attainment Scale (ICCAS) before/after the IPDEU experience. Pre/post composite ICCAS scores were analyzed by independent t-tests. Pre/Post individual item Likert responses were dichotomized and analyzed using Chi Square.

**Results:** Fifty students completed the experience. Twenty-seven (54%) reported prior formal IPE. Composite ICCAS scores improved post-IPDEU (65.3 vs 81.5, p<0.0001). Pre-IPDEU, few students rated individual competencies highly (<70% rated themselves Very Good or Excellent on any item). Post-IPDEU, all item competency ratings improved (p-values ranged 0.02 to <0.0001). Areas of greatest improvement were IP team utilization, communication, roles, and providing constructive team feedback. Sample size limited subset analyses.

**Conclusion:** Despite most students reporting prior IPE exposure, few IP competencies were rated highly at baseline. All competency ratings improved significantly post-IPDEU, suggesting the experience improved confidence in knowledge, skills, or both. Next steps will assess long-term competency retention, evaluate differences in outcomes by profession and level of pre-existing clinical experience, explore thematic content of student debriefs, and gauge scalability of the model.
**Introduction:** Interprofessional (IP) collaborative practice is essential for older adults with complex medical problems and improves health outcomes. Interprofessional education (IPE) is required for students across the health professions, but many preceptors remain untrained in IP practice and instruction. After formal needs assessment, we designed an integrated IP practice + IPE instructor skills training to prepare preceptors to teach IPE competencies to health profession students in the clinical setting.

**Methods:** Ten health professionals (5 nurse, 2 physical therapy, 2 occupational therapy, 1 speech therapy) at a major academic medical center neurotrauma unit [designated the Interprofessional Dedicated Education Unit (IPDEU)] were trained as IPE instructors in Jul-Aug 2018. IPE instructor training focused on IP practice skills and IPE-specific Instructor skills. IP practice training included 1) a 1-hour web-based skills module based on the 2016 Interprofessional Education Collaborative Core Competencies, and 2) a 2-hour simulated physician colleague interaction for IP skill practice. IPE-specific instructor training included 1) a 1-hour web-based module emphasizing skills to facilitate active IPE-directed observation by students, and 2) a 2-hour simulated IP student interaction for instructor skill practice. We measured pre-post change in IP practice and instructor knowledge (multiple-choice test), IP attitudes [Interprofessional Collaborative Competency Attainment Scale (ICCAS) & Assessment for Collaborative Environments (ACE15)], and IP practice/instructor skills (simulation skill checklists). Composite scores for each measure were analyzed using paired t-tests.

**Results:** Nine participants had complete data. ICCAS & ACE15 scores increased after training (diff 7.8, p=0.011; 12.2, p=0.049, respectively). Both IP practice and IP instructor skills increased after training, with a greater increase in instructor skills (diff 1.86, p=0.0626; 2.99,p=0.026, respectively). Knowledge test scores were unchanged.

**Conclusion:** All measures improved after training, with the exception of knowledge test scores, which were unchanged. Improvement in IPE instructor skills suggests IPE-specific teaching is a new skill that improves with training. Baseline self-rated IP competencies (ICCAS) were higher than was reflected in baseline skill use, indicating a discrepancy between confidence and competence. Both self-rated IP competencies and skill use improved with training. In this preliminary study, dedicated IPE instructor training was feasible and improved instructors’ IP competency ratings and skill use. Results highlight the need for and potential impact of formal training for instructors facilitating IPE for health profession students. Next steps include evaluation of student outcomes and implementation on a larger scale.
**Poster: The Hypothesis-Driven Physical Exam for Common Inpatient Presenting Symptoms**

**Presenter:** Allison Kanakis, Clinical Fellow

**Research Interest:** Medical Education
General Internal Medicine

**Mentors:** Deborah DiNardo MD

**Authors:** Allison Kanakis MD, Deborah DiNardo MD, Eliana Bonifacino MD, Melissa McNeil MD

**Introduction:** The declining emphasis on the physical exam in medical education and in clinical practice has been widely recognized. More recently, there has been a renewed interest in physical diagnosis as an essential component of medical decision-making. As opposed to the complete “head-to-toe” physical exam, the hypothesis-driven physical exam (HDPE) involves predicting and recognizing specific physical exam findings to refine differential diagnoses. However, there is a lack of consensus regarding the essential elements in a HDPE across a spectrum of disease processes and learner levels. We therefore aimed to develop a rubric for assessing the medical student HDPE for common inpatient presenting symptoms.

**Methods:** We reviewed 248 admission notes submitted by 67 medical students at the University of Pittsburgh Medical Center for documentation of chief complaints. We selected the 3 most common chief complaints as presented in the students’ admission notes. For each of these 3 selected symptoms, four clinical reasoning experts generated a list of the most common associated diagnoses and the relevant diagnostic physical exam maneuvers based on clinical experience and literature review. We then created a survey to administer to a group of clinical reasoning and physical diagnosis experts. In the first part of the survey, participants rank how important it is to perform physical exam maneuvers for each symptom on initial assessment using a Likert scale. In the second part of the survey, participants identify whether or not an exam maneuver should be performed only if a specific diagnosis is being considered using a dichotomous scale. We plan to conduct a two-round Delphi to establish a consensus list of essential physical exam maneuvers for the HDPE for the 3 selected symptoms.

**Results:** The 3 most common chief complaints were shortness of breath (32 patients), abdominal pain (23 patients), and chest pain (21 patients). These 3 chief complaints comprised 76 (31%) of submitted admission notes. Based on literature review and expert group consensus as described, we will consolidate the list into physical exam maneuvers that (1) should always be performed for a particular presenting symptom and (2) should be done in a hypothesis-driven manner if a specific diagnosis is being considered.

**Conclusion:** By developing a rubric for common inpatient presenting symptoms, the teaching and evaluation of the inpatient HDPE in medical students can be standardized. This tool has the potential to help students learn the pertinence of physical exam findings and enhance their clinical reasoning skills.
104-A  Poster: A Robust Faculty Development Program for Medical Educators: A Decade of Experience

Presenter: Sarah Merriam, Junior Faculty

Research Interest: Medical Education
General Internal Medicine

Mentors: Carla Spagnoletti MD

Authors: Sarah Merriam MD, Rachel Vanderberg MD, Melissa McNeil MD, Tanya Nikiforova MD, Carla Spagnoletti MD

Introduction: Faculty development programs (FDPs) foster learning communities and enhance professional identity formation. Recent work has highlighted the need to consider competency-based frameworks when designing FDPs, to both identify deficiencies in existing curricula and to drive skill development across clinical practice, teaching, and scholarship domains. We aim to outline the components of a novel FDP in the context of established medical educator competencies, describe its outcomes to date, and identify steps for implementation of similar programming.

Methods: The FDP consists of 4 one-hour-long conferences held weekly since 2007 at the University of Pittsburgh SOM, open to all health sciences faculty, fellows, and others interested in medical education. Evaluation data is available for faculty attendees and presenters in 4 consecutive academic years from 2014 to 2018. The overarching goal of the FDP is to support the advancement of educator faculty, promote curricular innovation and teaching excellence, enhance educational scholarship, and cultivate a community of educators. The FDP includes four rotating conferences: Academy of Master Educators Seminar Series, Medical Education Research Conference, Medical Education Journal Club, and Medical Education Research Methods and Innovative Design Conference. We outlined the relationship of these conferences to established medical educator competencies by consensus. We also evaluated 1) presenter and attendee rank and department, 2) average conference attendance over 4 academic years (2014-2018) and 3) impact of this program on faculty presenters.

Results: Collectively, this well-attended (average # of attendees per conference = 20) internally-driven FDP meets all established competencies for educator faculty. Presenters and attendees were diverse in terms of academic rank and represented 12 clinical and 7 basic science departments, dental medicine and physical therapy. Of research works presented from 2014-2017, 14 peer-reviewed publications resulted, with an additional 5 manuscripts in revision or under review. Because presenters and attendees are volunteers, the FDP’s 10-year track record is evidence of faculty satisfaction with the programming. We have identified key factors for implementation of similar FDPs: establish a clearly defined mission statement that meets the needs of the target audience and engenders engagement and ownership, identify champion(s) to lead the effort, capitalize on local talent and expertise, and secure institutional backing.

Conclusion: This integrated FDP capitalizes on existing local resources to foster a community of medical educators. With its focus on fostering educator skills across a continuum, it provides a valuable framework for the growth and academic achievement of medical educators.
**Poster Abstracts**

105-A **Poster:** Perspective-Taking in medical education: A Qualitative Analysis of Internal Medicine Residents’ Attitudes of a Novel Curriculum

**Presenter:** Brianna Rossiter, Clinical Fellow

**Research Interest:** Medical Education
  General Internal Medicine

**Mentors:** Melissa McNeil MD

**Funding Source:** Shadyside Foundation

**Authors:** Brianna Rossiter MD, Melissa McNeil MD, Gaetan Sgro MD

**Introduction:** Residency is marked both by intense knowledge acquisition, personal growth, and by increasing levels of burnout and cynicism. The latter erode empathy and undermine the altruistic motivations that led to a medical career path. Interactions with so-called “challenging” patients in the ambulatory setting are often cited as drivers of burnout and cynicism. Perspective-taking (PT) is a cognitive skill defined as “an understanding of other people’s mental states” and has been studied as a way to cultivate empathy. The purpose of this study was to explore internal medicine residents’ attitudes to the implementation of a PT exercise in an ambulatory curriculum.

**Methods:** The PT curriculum took place within the PGY3 ambulatory rotation within the UPMC Internal Medicine Residency, which all PGY3 residents complete as part of their training. The curriculum included a PT writing exercise itself and a facilitator-guided, de-brief session. Residents were then invited to participate in an interview to explore their attitudes to the curriculum. Two researchers developed a code book based on the interviews, coded, and assessed inter-rater reliability. Thematic analysis was completed with consultation of a qualitative research group.

**Results:** Thirteen residents completed interviews and were analyzed. Preliminary emerging themes include: appreciation for a novel approach to understanding challenging patients, ambivalence over the best way to engage in self-reflection in medical training, finding value in peers’ contribution to the de-brief session, identification of PT as a way navigate challenging patient interactions, and defining empathy as an extremely important characteristic of a physician.

**Conclusion:** A clinical experience in PT, encouraging resident reflection, provides a novel approach for probing empathy, a challenging construct to teach in medical education. Residents appreciated the opportunity to reflect about challenging patient encounters and found value in de-briefing with their peers. These attitudes support the need for future work in using PT as a cognitive means for maintaining empathy in medical training.
106-A  **Poster:** Career consequences for medical students experiencing sexual harassment differ by gender and type of exposure

**Presenter:** Emmanuelle Yecies, Clinical Fellow

**Research Interest:** Medical Education  
General Internal Medicine

**Mentors:** Melissa McNeil MD

**Authors:** Emmanuelle Yecies MD, Melissa McNeil MD

**Introduction:** Recent studies have demonstrated the high prevalence of sexual harassment in medicine, with 30% of female physicians and 15% of medical students reporting sexual harassment. However, the consequences that sexual harassment has on the attitudes and career trajectories of women in medicine remain unclear. We hypothesized that 1) sexual harassment would affect female students’ attitudes towards the medical profession more than their male counterparts; and 2) these experiences would cause women to have negative attitudes towards their work and impact their specialty choices.

**Methods:** An in-person cross-sectional survey assessing experience with sexual harassment during medical school was administered to incoming interns at UPMC. The survey was adapted from a validated instrument and included questions about exposure to different types of sexual harassment and demographics. Three questions were included to explore attitudes and behaviors following experiences of sexual harassment. Attitudes were analyzed to determine differences between male and female respondents. Additional analysis was performed to determine whether exposure to certain types of sexual harassment was more strongly associated with attitude changes.

**Results:** 199 incoming interns who graduated from medical schools spanning 32 states returned the survey (100% response rate), with 198 completing both demographics and attitudes sections. Of these, 99 respondents identified as female, and 99 as male. Women were more likely than men to report that negative experiences related to their gender caused them to feel bad about coming to work, to doubt their choice of medicine as a profession, and contributed to changing the specialty they pursued. (p<0.001 for all). Of those respondents who shared which specialty they switched from, men exclusively identified Obstetrics-Gynecology (3/3), while women identified various specialties (5/9 identified surgical fields). The types of sexual harassment associated with attitude changes differed in men and women. For women, exposure to a hostile environment was associated with doubting medicine as a profession (p=0.016) and switching their specialty (p=0.013). Severe harassment was associated with feeling bad about going to work (p<0.001). In contrast, the three types of attitude changes in men were solely related to experiencing assumptions of traditional gender roles (p=0.002, p=0.007, and p=0.02).

**Conclusion:** Though students of both genders reported career consequences to negative gender-related experiences, women identified these more frequently. These experiences affected specialty choice, including some women moving away from surgical fields. Because exposure type may affect students differently, it will be important to develop targeted reporting and support systems to allow all students to thrive in medicine.
107-A  **Poster:** From the #MeToo Frontlines: Incoming Interns Report a Breadth of Experiences Related to Sexual Harassment in Medical School

**Presenter:** Emmanuelle Yecies, Clinical Fellow

**Research Interest:** Medical Education  
General Internal Medicine

**Mentors:** Melissa McNeil MD

**Authors:** Emmanuelle Yecies MD, Melissa McNeil MD

**Introduction:** The prevalence of sexual harassment in medicine has recently been in the spotlight, with up to 30% of female physicians reporting sexual harassment in the workplace. There is also increasing recognition that the spectrum of sex discrimination includes microaggressions, the prevalence of which have yet to be elucidated. Medical students are a particularly vulnerable population within medicine as they experience the widest power differentials and their ongoing grades and evaluations deepen the consequences of retaliation to reporting. With the influence of the #MeToo movement, a few medical school deans have seen an increase in reporting, but most schools report stagnant (and low) reporting rates, indicating that sexual harassment may still be under-represented in the current reporting system. We aimed to study the ways in which medical students experienced sexual harassment in medicine.

**Methods:** An in-person cross-sectional survey was administered to incoming interns at UPMC about their experience with sexual harassment in medical school. An optional question invited respondents to share experiences of sexual harassment in free-text form. The reports were examined for common themes.

**Results:** 185 graduates of U.S. medical schools returned the survey, with 42 completing the optional free-text question (“If you are willing and interested in sharing any of your experiences, please use the space below”). Of these, 33 respondents identified as female, and 9 as male. Analysis of the responses revealed six recurring themes: (1) decision not to report, (2) unsuccessful reporting, (3) disproportionate “scut” work for female students, (4) inappropriate comments and touching, (5) repeat offenders with well-known reputations, and (6) male patients harassing female students. This last theme was particularly attributed to Veterans Administration (VA) patients.

**Conclusion:** More female students than male students shared negative experiences. They identified a breadth of experiences attributed to both colleagues/superiors and patients. Most importantly, many students identified the current reporting system as discouraging of reporting. Given the variety of experiences shared by incoming trainees, tackling sexual harassment must evolve from a single broad campaign to targeted approaches for each of these issues. The current reporting system appears to be insufficient and reforms are needed to develop an improved system that encourages and supports trainees to report inappropriate experiences.
**Poster: The effect of renal inpatient service size on inpatient renal related medication safety recommendations**

**Presenter:** Huiwen Chen, Clinical Fellow

**Research Interest:** Quality Improvement  
Renal-Electrolyte

**Mentors:** Ranil Desilva MD

**Authors:** Huiwen Chen MD, Syeda Ahmad MD, Ranil Desilva MD, James Johnston MD

**Introduction:** Delivery of quality care is one of the highest goals for most medical institutions. However, quality care is difficult to define but has been linked with adequate staff to patient ratio, timely care, interdisciplinary communication and medical error reduction. In emergency departments, studies have found that nurse-to-patient ratio range less than 1:4 is associated with significant wait time reduction. In intensive care units, physician-to-patient ratios greater than fourteen and nurse-to-patient greater than two have been associated with higher patient mortality. Our study objective is to assess the impact of nephrology consult service size on medication safety. We hypothesize a larger service size is more likely to lead to compromised patient care in the form of errors involving renal related recommendations regarding following 4 categories: antibiotic dosing, the presence of nephrotoxic agents, renal adjustment of neuroleptic medications and correction of electrolyte abnormalities.

**Methods:** This is a retrospective study reviewing patients' charts based on general nephrology consults placed in UPMC Presbyterian and MUH from Jan 1st 2018 to December 13th 2018. Patients with functional allografted kidney and patients who were admitted in the Magee Women's hospital will be excluded from this study. Criteria for chart review was standardized and a rubric was generated prior to the research. Reviewers were trained to evaluate renal medication recommendation based on the rubric. Staff schedule during January 2018 and December 2018 was also obtained. The association of medication error from consult notes and total service size will be calculated by a statistician at the Wolff Center. The association of medication error in the progress notes and the total service size will also be assessed.

**Results:** Pending result.

**Conclusion:** A large nephrology service size is associated with compromised patient care in the form of overlooked medication errors. In order to reduce medication error, we will need to consider options such as incorporating additional mid-level provider or a renal pharmacist into our team when the service volume is higher than usual.
INTRODUCTION: Colonoscopy and Fecal Immunochemical Testing (FIT) are preferred modalities for colorectal cancer (CRC) screening. Appropriate FIT testing requires that negative tests be repeated annually, positive tests lead to a diagnostic colonoscopy, and FIT should not be performed within 5 years of a colonoscopy with adequate bowel preparation. We studied the frequency of inappropriate FIT testing at the VA Pittsburgh HealthCare System (VAPHS).

METHODS: The VAPHS data repository was queried for all patients who underwent a FIT in a 3-year period (2015-2017). We calculated the following: 1) The rate of a negative FIT in 2015/2016 followed by a second FIT in 2016/2017 in a random selection of patients (3% margin of sampling error, 95% confidence interval [CI]). Demographics were compared in an equal random number of patients with and without follow up FIT (subset=5% margin of sampling error, 95% CI of all negative FIT). 2) Rate of completing colonoscopy following a positive FIT in a random selection of patients (3% margin of sampling error, 95% CI). 3) FIT following a colonoscopy for all patients.

RESULTS: A total of 6766 FIT were performed in the interval; 4391 unique patients had at least one negative FIT and 709 patients had a positive FIT. 1) In 1742 patients with at least one negative FIT, 870 patients were eligible for repeat FIT during the 3-year period and only 543 (62.4%) underwent at least two FIT. There were no significant demographical differences between the two groups 2) In 410 patients with positive FIT, 113 (27.5%) did not undergo a colonoscopy within one year due to patient refusal, or failure to schedule or keep colonoscopy appointment. There were no significant differences between the group demographics. 3) In 832 patients who had both a FIT and colonoscopy, 108 patients underwent colonoscopy with a subsequent FIT. Of these, 95 (88%) were judged to be inappropriate (CRC screening 38, anemia 23, GI symptoms 32, and unclear indications 2), and 13 FIT were appropriate (switched from colonoscopy to FIT as patient preferred screening method).

CONCLUSION: In this single healthcare system experience, a large percentage of patients underwent inappropriate FIT testing due to 1) failure to undergo serial FIT after a negative result (37.6%), 2) failure to complete colonoscopy following a positive FIT (27.5%), or 3) undergoing inappropriate FIT following a recent colonoscopy. Efforts are required to improve both patient and provider adherence to appropriate CRC screening.
**111-A**  **Poster:** Dirty Urine: A Brief Intervention to Decrease Urine Culture Contamination Rates

**Presenter:** Alison O'Donnell, Clinical Fellow

**Research Interest:** Quality Improvement  
Geriatric Medicine

**Mentors:** John Naumovski MD

**Authors:** Alison O'Donnell DO, Pratik Pandit MD, Kate Bowers, John Naumovski MD

**Introduction:** Accurate diagnosis of UTI in nursing home (NH) settings is difficult as different criteria are frequently used, and empiric treatment based on clinical judgment is common. Additionally, urine cultures are heavily relied upon, although asymptomatic bacteriuria and bacterial contamination from poor collection and handling technique is common. In some studies, bacterial contamination has been noted in over 30% of positive urine cultures in patients with elevated body mass index (BMI) (Zwank & Bourdon, 2016). NH residents often have additional risk factors, including decreased mobility, bowel and bladder incontinence, and cognitive impairment, which can lead to contaminated urine cultures. Urine culture contamination can lead to unnecessary and inappropriate antibiotic use, resulting in adverse events and antibiotic resistance. Therefore, efforts should be made to ensure that urine samples are collected and handled using the proper technique. We sought to examine whether implementation of a urine collection protocol utilizing chlorhexidine-containing genital region cleansing wipes decreased urine culture contamination rates.

**Methods:** Charles Morris Center for Rehab and Nursing is a 159-bed nonprofit nursing facility divided approximately equally between short-stay (i.e. rehabilitation) and long-term care, with a locked dementia unit comprising one of its four main wings. Providers and staff were educated on proper urine sample collection technique with educational materials. A simple bedside kit including a sterile urine specimen cup and genital wipes was developed for urine collection for use by the staff. Patient baseline demographics, urinary symptoms, urinalyses, and urine culture results were collected and analyzed.

**Results:** Our preliminary data are modest, but show a low rate of contamination in this initial sample collection. In the initial three months of this intervention, only one of 16 urine cultures (6.3%) was found to be contaminated. Further post-intervention data is pending and will be available at the time of presentation.

**Conclusion:** It is difficult to obtain a reliable clean-catch urine in older nursing home residents. Urine bacterial contamination is high, which should be suspected if there is growth of multiple bacteria with less than 100,000 colony-forming units. Efforts to minimize contamination of urine samples, including proper collection technique with use of genital wipes and proper handling of urine samples, are effective and should be implemented with the goal of ultimately decreasing unnecessary antibiotic use.
Introduction: Fluoroquinolones are often used as first-line treatment of urinary tract infections (UTI). However, given high local resistance rates of E. coli to fluoroquinolones, risk of adverse events including black box warnings on use, and published guidelines recommending the use of other agents, we sought to examine the impact of a multifaceted antimicrobial stewardship campaign over time to determine the sustainability of the intervention and maintenance of outcomes.

Methods: Charles Morris Center for Rehab and Nursing is a 159-bed nonprofit nursing facility. An antimicrobial stewardship campaign utilizing educational materials for patients, family, staff, and providers was disseminated to all staff and providers at the facility through in-service lectures to staff and printed handouts for providers. Monthly reports of urine cultures and sensitivities and antibiotic use were reviewed and shared with providers, specifically the frequency of fluoroquinolone prescriptions. Patient demographic data, clinical symptoms, urinalyses, urine cultures, and antibiotic use in residents who underwent treatment for UTIs were analyzed.

Results: In the one-year study period, the multifaceted antimicrobial stewardship campaign utilizing educational materials for patients, family, staff, and providers on fluoroquinolone use was effective at decreasing fluoroquinolone use from 49.3% to 27%. However, at two years post-intervention, the use of fluoroquinolones for the treatment of UTI, confirmed or suspected, again approached previous rates up to 43.8%.

Conclusion: An antimicrobial stewardship campaign based mainly on educational initiatives did not sustain initially favorable results at two years, and fluoroquinolones once again became the most frequently prescribed first-line therapies. This suggests the need for continued education and alternative and more sustainable approaches to maintain appropriate antibiotic use. As a result, this ongoing quality improvement project subsequently increased efforts to reeducate patients, family, staff, and providers and implemented provider order sets to help guide clinicians towards appropriate antibiotic therapy as a more durable and sustainable antimicrobial stewardship initiative.
Poster: Management of Bone Pain from "Metastatic" Sarcoidosis

Presenter: Alison O'Donnell, Clinical Fellow

Research Interest: Quality Improvement
Geriatric Medicine

Mentors: Sangeeta Rana MD

Authors: Alison O'Donnell DO, Sangeeta Rana MD

Introduction: Chronic arthritis resulting from sarcoidosis is uncommon and found in less than two percent of patients with sarcoidosis. While it typically occurs in the hands, feet, and ankles, there are a few cases of biopsy-proven pelvic and sacral sarcoidosis described in the literature. General management of chronic arthritis in patients with sarcoidosis is typically with anti-inflammatory medications and disease-modifying antirheumatic drugs. There is little guidance on pain management in patients with chronic pain refractory to these therapies.

Methods: Our goal is to describe a interdisciplinary team approach to chronic pain management in a complex patient with bone pain from sarcoidosis.

Results: A 69-year-old Caucasian male nursing home resident with “metastatic” sarcoidosis resulting in pulmonary disease, chronic systolic heart failure, chronic kidney disease, and biopsy-proven painful bone lesions of the hips and pelvis with a history of opioid use disorder, mild cognitive impairment, anxiety, and insomnia presented with chronic pain in the setting of delirium, falls, and progressive decline. Given his presentation, pain management in this patient required a multidisciplinary approach. Our geriatrics team consulted with rheumatology, psychiatry, and pain management. The patient's sarcoidosis was managed with hydroxychloroquine. A pain management regimen consisting of physical therapy, acetaminophen, low-dose opioids, lidocaine patches, topical diclofenac, duloxetine, and low-dose gabapentin was developed to maximize pain control while balancing the risks of worsening delirium and future falls. Additionally, due to the advanced and progressive nature of the patient's sarcoidosis and associated complications, multiple discussions were held with the patient's family to address goals of care.

Conclusion: We highlight a geriatric nursing home resident with mild cognitive impairment and multiple medical comorbidities including systemic sarcoidosis and refractory pain, where pain control was achieved using interdisciplinary team approach, minimizing opioids and maximizing patient comfort pursuant to family goals. The approach as outlined in our case can decrease the risk of delirium and falls that are associated with high-dose opioids.
**114-A Poster:** Hydroxychloroquine: repurposing an old drug as a new treatment for diabetes mellitus

**Presenter:** Samina Afreen, Clinical Fellow

**Research Interest:** Translational Endocrinology and Metabolism

**Mentors:** Frederico Toledo MD

**Funding Source:** American Diabetes Association, UPP Foundation

**Authors:** Samina Afreen MD, James DeLany PhD, Rachel Miller PhD, Samannaazz Khoja PhD, Yingze Zhang PhD, Frederico Toledo MD

**Introduction:** Type 2 diabetes (T2D) affects 10% of adults in the US, a four-fold increase since 1980. Therefore, new and inexpensive treatments for T2D would have a major impact on public health. Insulin resistance is a core pathophysiological defect in the pathogenesis of T2D and drugs that improve insulin resistance can prevent and treat T2D. However, only two medications are currently approved for insulin resistance and each has its own shortcomings. No new treatments have been approved since 1999. Hydroxychloroquine-sulfate (HCQ) reduces inflammatory activity and is employed in the treatment of lupus and rheumatoid arthritis. Interestingly, patients treated with HCQ have a lower incidence of T2D, suggesting a favorable effect on glucose homeostasis that could be exploited in T2D. However, the underlying physiological mechanisms are unknown. The goal of this study was to determine the effect of HCQ on the key tissues responsible for insulin resistance in humans and the effects of HCQ on adipose tissue inflammation, which has been implicated in the pathogenesis of insulin resistance.

**Methods:** Hypothesis: HCQ enhances insulin sensitivity through metabolic changes in skeletal muscle, liver and adipose tissue. Methods: We conducted a mechanistic, randomized, double-blinded, placebo-controlled trial. Treatment consisted of HCQ PO 400 mg/day vs. placebo for 13 weeks. Volunteers (n=34) were overweight/obese men and women with insulin resistance but without diabetes or autoimmune diseases. The primary outcome was a change from baseline in whole-body insulin sensitivity. Secondary outcomes were: a) insulin sensitivity of muscle, liver and adipose tissue measured by hyperinsulinemic-euglycemic clamps with stable-isotope tracers; b) circulating adipokines and inflammation biomarkers; c) adiposity (total and regional) assessed by DXA and CT scan image analysis.

**Results:** Whole-body insulin sensitivity was improved by HCQ, but not placebo (33.1% vs 3.84%, P=0.036). This effect was accounted for by changes in insulin sensitivity of skeletal muscle, without changes in liver. In plasma, HCQ lowered IL-6 (P=0.011) and increased adiponectin (P=0.45). HCQ had no impact on total adiposity, regional fat distribution, and adipose tissue insulin sensitivity.

**Conclusion:** HCQ enhances whole-body insulin sensitivity by a new mechanism that selectively targets skeletal muscle. This mechanism appears to be independent of adipose tissue insulin sensitivity, adipose tissue mass or regional distribution. However, observed changes in the adipokine profile suggest that HCQ modulates adipose tissue inflammation. Detailed studies of adipose tissue biopsy samples are ongoing. HCQ may be a viable insulin-sensitizer drug for the prevention/treatment of T2D.
Introduction: Mucin 1 (human MUC1, mouse Muc1) is expressed on the apical surface of most epithelial cells, including the thick ascending limb (TAL) and distal nephron segments. Proximal tubular expression of Muc1 is induced in ischemia-reperfusion injury, where it stabilizes HIF-1a and b-catenin and plays a protective role. A frame-shift mutation in MUC1 causes autosomal dominant tubulointerstitial kidney disease. However, there is limited information regarding its functional role in normal kidney. Muc1 knockout mice have no clear phenotype in the absence of stressors (e.g. bacterial infection). The TRPV5 Ca2+ channel was reported to be stabilized on the cell surface by galectin-dependent cross-linking to MUC1, providing a novel mechanism for regulation of this ion channel. We observed robust Muc1 apical and sub-apical staining in type A and type B intercalated cells (ICs). In Type A ICs, Muc1 co-localizes with the vacuolar H+ ATPase (V-ATPase), a protein complex that mediates apical ATP-driven H+ secretion. V-ATPase subcellular localization regulates H+ secretion, while defects in V-ATPase function can cause renal tubular acidosis. As Muc1 and the V-ATPase are highly expressed in ICs, we tested the hypothesis that Muc1 regulates V-ATPase expression and function.

Methods: Muc1 KO (Muc1-/-), Muc1 heterozygous (Muc1+/-) and control mice were given 2.5% sucrose with or without 0.28 M NH4Cl in drinking water for 7 days. Plasma electrolytes, urine pH and NH4+ were measured. Kidneys were processed for immunoblotting and confocal immunofluorescence (IF) microscopy.

Results: IF staining of fixed mouse kidney slices revealed that Muc1 co-localizes with luminal V-ATPase in ICs. Moreover, V-ATPase moved from the cytosol to the apical surface when WT mice were subjected to an acid load. In contrast, V-ATPase remained cytosolic in Muc1-/- mice. In response to acid-loading, both Muc1-/- and Muc1+/- mice exhibited impaired urinary acidification while only Muc1 KO mice exhibited greater metabolic acidosis. The IC-specific a4-subunit of V-ATPase co-immunoprecipitated with Muc1 in extracts of mouse kidney, suggesting that they are components of a protein complex.

Conclusion: These results suggest that Muc1 interacts with the V-ATPase and influences its cell surface localization in type A ICs, and is necessary for a normal renal response to an acid load.
116-A  Poster: Mucin 1 Regulates KIM-1 Function Following Ischemic Renal Injury

Presenter: Mohammad Al-bataineh, Junior Faculty

Research Interest: Translational Renal-Electrolyte

Mentors: Rebecca Hughey PhD

Funding Source: K01

Authors: Mohammad Al-bataineh PhD, Carol Kinlough BSc, Zaichuan Mi MD, Edwin Jackson PhD, Rebecca Hughey PhD

Introduction: Kidney injury molecule-1 (KIM-1) is a type 1 transmembrane glycoprotein that is rapidly induced after kidney injury in the proximal tubule (PT). The ectodomain of KIM-1 is cleaved by a disintegrin and metalloproteinase domain 17 (ADAM17) and thereby constitutively shed into the urine providing a sensitive biomarker for kidney injury. It was reported recently that a transcription factor STAT3 is phosphorylated by ERK1/2 following kidney injury and thereby upregulates KIM-1. KIM-1 also has an anti-inflammatory role as it mediates phagocytosis of apoptotic and necrotic cells (efferocytosis) following kidney injury. However, the accelerated shedding of KIM-1 regulated by p38 MAPK blocks efferocytosis as the excess soluble KIM-1 acts as a decoy to cell-associated KIM-1. Mucin 1 (MUC1 in humans, and Muc1 in mice) is a transmembrane glycoprotein found primarily in the distal nephron that is also induced in the PT where it plays a protective role following kidney injury.

Methods: Using our hanging-weight protocol of 20 min ischemia and 48 h recovery, we observed a significant two-fold higher level of urinary KIM-1 as well as more severe kidney injury in Muc1 KO mice when compared to wild-type (WT) littermates. We also found that MUC1 and KIM-1 are co-localized in human kidney proximal tubule using immunofluorescence microscopy. Based on these findings, we tested the hypothesis that Muc1 limits kidney injury and enhances recovery during ischemia-reperfusion injury (IRI) by modulating the pathways known to regulate PT KIM-1 activity.

Results: Immunoblots of kidney tissue revealed that levels of active ERK1/2 were significantly higher in Muc1 KO mice when compared to WT littermates. Though the levels of active p38 MAPK were significantly induced following kidney injury, there was no significant difference between Muc1 KO mice and WT littermates. Using an in vitro cell culture model where MDCK cells were stably transfected with KIM-1 and transiently transfected with MUC1 or empty vector, we observed a reduction in KIM-1 expression levels in the presence of MUC1. We also observed in our preliminary data that KIM-1 shedding was enhanced after treating MDCK cells with PMA (ADAM17 activator) only in the absence of MUC1.

Conclusion: As Muc1 is also a substrate for ADAM17, we also hypothesize that the absence of the competing Muc1 substrate after AKI in the Muc1 KO mice, could account for the accelerated shedding of KIM-1 and consequently more severe kidney injury. These results support the likelihood that Muc1 regulates KIM-1 function by regulating both its expression and shedding following kidney injury.
Poster: Serum Wnt inhibitor DKK1 is associated with adiposity and insulin resistance in non-diabetic North Americans

Presenter: Hira Ali, Post-Doctoral Scholar

Research Interest: Translational Endocrinology and Metabolism

Mentors: Iva Miljkovic MD

Funding Source: T32

Authors: Hira Ali MD, Elizabeth Oczypok MD, Iva Miljkovic MD, Ryan Cvejkus MS, Joseph Zmuda PhD, James DeLany PhD, Erin Kershaw MD

Introduction: The Wnt pathway is known to influence body composition during human development by regulating bone formation, myogenesis and adipogenesis. We have recently shown that DKK1 is related to measures of adiposity in non-diabetic African ancestry males. Whether these relationships are true across sexes and/or other human populations remains unknown. In this study we evaluated the relationship of DKK1 with adiposity in a sample of male and female, mixed race, non-diabetic North American individuals.

Methods: Fasting serum DKK1 levels were measured using ELISAs in 201 non-diabetic subjects (age range 30.7–60 years, BMI range 19.9–64.0 kg/m2) recruited from the general population via television advertisement and mass mailing. The subjects were predominantly female (85%) and Caucasian (63%). Anthropometrics were obtained and markers of inflammation and glucose metabolism were measured from fasting serum samples. Spearman and partial Spearman correlation analysis was used to determine the association of DKK1 with measures of adiposity and insulin resistance.

Results: Circulating DKK1 was positively associated with BMI (r=0.30, p<0.001) and waist circumference (r=0.25, p<0.001), independent of age, race and sex. In addition, DKK1 was positively associated with fasting serum insulin level (r=0.18, p<0.01) and HOMA-IR (r=0.19, p<0.01) in age, sex and race adjusted models. However, these associations were no longer significant after adjustment for BMI.

Conclusion: This is the first study looking at correlation of DKK1 with adiposity in North American non-diabetic individuals. Our findings suggest that the link between DKK1 and insulin resistance maybe mediated indirectly through total and regional adiposity and that DKK1 could be a potential early biomarker for diabetes in high risk individuals. These findings support our findings in African ancestry males and add to the evidence favoring potential role of Wnt modulators in adiposity regulation in humans.
Poster: PVR triggers CD226 internalization and degradation by NK cells in metastatic melanoma.

Presenter: Joe-Marc Chauvin, Post-Doctoral Fellow

Research Interest: Translational
   Hematology/Oncology

Mentors: Hassane Zarour MD

Authors: Joe-Marc Chauvin PhD, Mignane Ka PhD, Ornella Pagliano BS, Carmine Menna BS, Cindy Sanders BS, Diwakar Davar MD, Soldano Ferrone MD, John Kirkwood MD, Alan Korman PhD, Hassane Zarour MD

Introduction: CD226 is a costimulatory receptor that mediates tumor recognition by NK cells and that competes with the inhibitory receptor TIGIT for binding to PVR (CD155) and CD112. CD226 is downregulated by tumor-infiltrating NK cells (TiNKs) in lung, ovarian and breast tumors, which express PVR. We have also previously shown that melanoma-infiltrating CD8+ T cells upregulate TIGIT and downregulate CD226, resulting in the imbalance of TIGIT/CD226 expression. Here we wanted to evaluate the expression of TIGIT and CD226 by TiNKs in metastatic melanoma and the role of PVR in modulating TIGIT and CD226 expression in the tumor microenvironment.

Methods: Flow cytometry analysis was used to evaluate the phenotype and the function of NK cells in the periphery (cNKs) and tumor sites. CD226 mRNA was evaluated by RT-PCR. CD226 and TIGIT internalization was evaluated on isolated cNKs by Imagestream analysis.

Results: In sharp contrast with CD8+ T cells, TiNKs downregulate both TIGIT and CD226 with a strong decrease of CD226 level of expression as compared to cNKs. TiNKs exhibit decreased expression of activation markers, lytic potential and NK cell-mediated melanoma killing as compared to cNKs. Membrane-bound PVR, but not soluble PVR, triggers CD226 internalization and degradation. The levels of CD226 and TIGIT expression by NK cells inversely correlate with the level of PVR expression by melanoma cells.

Conclusion: TiNKs exhibit decreased function and decreased expression of TIGIT and CD226 in contrast to cNKs. PVR expressed by melanoma cells induces TIGIT internalization and CD226 degradation by NK cells. Our data suggest that PVR plays a critical role in the tumor microenvironment in contributing to NK cell dysfunction by modulating CD226 expression.
119-A Poster: Measuring the single-cell heterogeneity in the skin tumors of patients with cutaneous T cell lymphoma

Presenter: Alyxzandria Gaydosik, Research III

Research Interest: Translational Rheumatology and Clinical Immunology

Mentors: Patrizia Fuschiotti PhD

Funding Source: R21 CA209107-02

Authors: Alyxzandria Gaydosik BSc, Tracy Tabib BSc, Larisa Geskin MD, James Conway PhD, Robert Lafyatis MD, Patrizia Fuschiotti PhD

Introduction: The heterogeneity of tumor cells presents a major challenge to cancer diagnosis and therapy. Cutaneous T cell lymphomas (CTCL) are a group of T lymphocyte malignancies that primarily affect skin. Lack of highly specific markers for malignant lymphocytes prevents early diagnosis, while only limited treatment options are available for patients with advanced-stage CTCL. Droplet-based single-cell transcriptome analysis of CTCL skin biopsies opens avenues for dissecting patient-specific T lymphocyte heterogeneity, providing a basis for identifying specific markers for diagnosis and cure of CTCL.

Methods: Single-cell RNA-sequencing was performed by Droplet-based sequencing (10X Genomics), focusing on 14,056 CD3+ lymphocytes (448 cells from normal and 13,608 cells from CTCL skin samples) from skin biopsies of 5 patients with advanced-stage CTCL and 4 healthy donors. Protein expression of identified genes was validated in advanced-stage CTCL skin tumors by immunohistochemistry and confocal immunofluorescence microscopy.

Results: Our analysis revealed a large inter- and intra-tumor gene expression heterogeneity in the T lymphocyte subset, as well as a common gene expression signature in highly proliferating lymphocytes that was validated in multiple advanced-stage skin tumors. In addition, we established the immunological state of reactive lymphocytes and found heterogeneity in effector and exhaustion programs across patient samples.

Conclusion: Single-cell analysis of CTCL skin tumor samples reveals patient-specific landscapes of malignant and reactive lymphocytes within the local microenvironment of each tumor, giving an unprecedented view of lymphocyte heterogeneity and identifying tumor-specific molecular signatures, with important implications for diagnosis and personalized disease treatment.
120-A  Poster: TIGIT+ Vδ-1 T cells exhibit strong antitumoral activity in melanoma.

Presenter: Mignane Biram Ka, Post-Doctoral Associate

Research Interest: Translational
Hematology/Oncology

Mentors: Hassane Zarour MD

Funding Source: BMS grant

Authors: Mignane KA PhD

Introduction: γδ T cells represent a small subset of innate cells in the peripheral blood (1–10% of T cells). γδ are enriched in epithelial tissues, where they recognize stress-associated proteins, heat shock proteins, and lipids. In healthy donors, gamma delta-2 (Vδ2) represent the majority of circulating γδ, and recognize non-peptide alkyl phosphates, such as isopentenyl pyrophosphate (IPP). Vδ1 represents the majority of γδ in epithelial tissues where they recognize stress-associated proteins (MIC-A/B), and CD1b-presented lipids. Multiple studies have shown the role of human γδ in cancer immunity. Human γδ exhibit lytic activity against cancer cell lines. The presence of γδ in multiple cancers appear to correlate with increased survival. The aim of this study is to evaluate the frequencies, phenotype and function γδT cells in patients with advanced melanoma.

Methods: Peripheral blood mononuclear cells (PBMCs) from 10 healthy controls (HD) and 30 melanoma patients (MP), and tumor-infiltrating lymphocytes (TILs) from 13 melanoma patients, were analyzed by flow cytometry ex vivo. γδT cells subsets were stimulated with PMA/ionomycin or cultured with melanoma cell lines prior to CD107a and cytokine production flow-based assays.

Results: Vδ1 frequencies are higher in MPs than HDs both in PBMCs and TILs. Vδ1 upregulate TIGIT in contrast to Vδ2. Interestingly, Vδ1 expressing TIGIT in PBMCs and TILs, is enriched in perforin and granzyme, and exhibits strong lytic activity against melanoma cells in vitro and in vivo. TIGIT represent the majority of the Vδ2 in the periphery and tumor sites.

Conclusion: Collectively, our findings show that Vδ1 frequencies are higher in MPs than HDs both in the periphery and at tumor sites. They also show that TIGIT+ Vδ1 exhibit strong anti-melanoma killing activity in vitro and in vivo.
121-A  Poster: Assessment of Brain Mitochondrial Function in a Septic Murine- Klebsiella Pneumoniae Model

Presenter: Sarah Kiel, Clinical Fellow

Research Interest: Translational
   Pulmonary, Allergy and Critical Care Medicine

Mentors: Bryan McVerry MD

Authors: Sarah Kiel MD, Faraaz Shah MD, Lia Edmunds PhD, Byron Chuan BS, Lanping Guo MD, Teresa Gallego-Martin PhD, Michael Jurczak PhD, Timothy Girard MD, Christopher O’Donnell PhD, Bryan McVerry MD

Introduction: Alterations in oxidative phosphorylation and mitochondrial function have been demonstrated in skeletal muscle, kidney, liver, and lung tissue in models of sepsis. However, in mice undergoing cecal ligation and puncture reported effects on mitochondrial respiration in the brain have been variable. In this study, we characterize mitochondrial respiration in brain tissue from mice infected with Klebsiella pneumoniae (KP).

Methods: 10 week old male C57BL/6] mice (n=14) were randomized to receive either KP (serotype ATCC43816, septic) or phosphate-buffered saline (control) via oropharyngeal aspiration. Pairs of mice, one septic and one control, were sacrificed 48 hours post inoculation. Brain cortex (n=14) and liver (n=8) tissue were harvested and homogenized on ice in specific mitochondrial respiration medium and analyzed using high resolution respirometry via the Oxygraph-2k Oroboros, (OROBOROS Instruments, Innsbruck Austria). Citrate synthase activity and total protein were quantified to control for active healthy mitochondria and tissue mass in all samples, respectively. Differences between septic and control groups were determined by paired sample t-test.

Results: Homogenized brain cortex from septic mice and control mice exhibited similar baseline oxygen consumption, NAD- and FAD-linked respiration, maximum electron transport system uncoupling respiration, and mitochondrial membrane permeability. The result remained consistent after adjustment for mitochondrial density (citrate synthase activity), and cellular/bacterial content (total protein). Similarly, addition of cytochrome c did not differentially alter mitochondrial membrane permeability between groups. In contrast, liver tissue from septic mice exhibited an increased NAD linked respiration, after citrate synthase correction, compared to controls, (188 ±8.0 vs.164.7 ± 4.3 pmol/s*mg*CS activity; p=0.040). Septic livers also displayed a decrease in oxygen consumption, after protein correction, during evaluation of maximal uncoupled respiration (41.0 ± 5.3 vs. 53.6 ± 3.9 pmol/s*mg tissue; p=0.047) suggesting mitochondrial function impairment.

Conclusion: These hypothesis generating data suggests that sepsis induced alteration of mitochondrial function is organ (and potentially complex) specific with differences detected in septic liver but not brain tissue. The lack of change in septic brain tissue may be due to multiple factors: subtle changes at the level of individual complexes may be obscured, anatomic regional specificity may exist, and the presence of Klebsiella pneumoniae in brain tissue may impact respiration analysis. Further work is required to assess individual complex activity, explore regional variability within the brain, and examine the contribution of bacteria on mitochondrial respiration in the septic brain.
**Poster Abstracts**

**122-A Poster:** Characterization of Exon 2 and 5 Skipping of TOLLIP gene and their Effects in the NF-kB Pathway

**Presenter:** Sharon Kim, Undergraduate Student

**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Yingze Zhang PhD

**Funding Source:** PACCM

**Authors:** Sharon Kim High School Diploma, Xiaoyun Li MD, Daniel Totten PhD, Sonia Feng High School Diploma, Brandon Guo High School Diploma, Yingze Zhang PhD

**Introduction:** Toll-interacting protein (TOLLIP) is one of the critical adaptor molecules in Toll-like receptor 4 (TLR4) signaling and serves as a negative regulator of NF-kB signaling pathway in cells challenged with high doses of LPS. Both animal models and mechanistic studies in recent years have yielded compelling data that support the anti-inflammatory role of TOLLIP. Genome-wide association study of idiopathic pulmonary fibrosis (IPF) patients also identified TOLLIP as one of the genes associated with IPF development and disease outcomes. Post-transcription regulation including alternative splicing has been described in mouse and human TOLLIP. However, little is known regarding the functional significance of alternative transcripts and the corresponding protein variants of TOLLIP. The goal of our study is to characterize the alternative splicing variants of TOLLIP proteins in regulating the NF-kB pathway, an important pathway in fibrosis development, using lung epithelial cells.

**Methods:** Total RNAs were extracted by TRIzol reagent from lung tissues of control and IPF patients. cDNAs were generated with a high-capacity cDNA reverse transcription kit (Applied Biosystems). Primer pairs were designed to amplify the TOLLIP transcripts across different exons. PCR products were cloned into Blunt TOPO vector and sequenced using Sanger sequencing. Full length human TOLLIP cDNA was amplified from normal cells and cloned into pcDNA3.1/v5-his topo vector. Splicing variants were generated from a WT clone by sequence-specific mutagenesis using Q5 Mutagenesis kit. Beas-2b cells were cultured using standard method and were cotransfected with TOLLIP WT or each of the variants individually, along with pGL4.32[luc 2P/NF-kB-RE/Hygro] vector (Promega), using Lipofectamine 2000. The pRL Renilla was used as an internal control. 6 hours before harvest, cells were treated with LPS or vehicle. Cell lysates were analyzed for luciferase activity using the DualLuciferase Assay System (Promega).

**Results:** We detected two major alternative transcripts: Exon 2 and Exon 5 skipping variants in human lung tissue. However, neither of them are exclusively expressed in normal or IPF lungs. Functionally, TOLLIP Exon 2 and Exon 5 skipping variants consistently resulted in a dramatic increase of NF-kB activation while WT-TOLLIP inhibited NF-kB activation when the Beas-2b cells were challenged with LPS.

**Conclusion:** Exon 2 and Exon 5 skipping in TOLLIP results in increasing NF-kB activation. These slicing variants may act as a competitive inhibitor of the wildtype TOLLIP function. Further characterization of these TOLLIP variants in different cell types and tissues will provide insight into their role in inflammatory regulation and lung fibrosis.
123-A  **Poster:** The Human Microbiome In Critical-Illness: Longitudinal Evolution Of Oral, Lung And Gut Communities In Mechanically-Ventilated Patients And Association With Clinical Outcomes.

**Presenter:** Georgios Kitsios, Junior Faculty

**Research Interest:** Translational  
   Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** K23

**Authors:** Georgios Kitsios MD, Rachel Nettles MS, Libing Yang MDc, Katherine Fair MDc, Shulin Qin MD, Adam Fitch MS, John Evankovich MD, William Bain MD, Daniel Dunlap MD, Faraaz Shah MD, Sarah Rapport MPH, Barbara Methe PhD, Janet Lee MD, Alison Morris MD, Bryan McVerry MD

**Introduction:** Significant changes in human microbial communities in the respiratory and intestinal tracts have been described with critical illness, including low alpha-diversity and overgrowth of potential pathogenic bacteria. However, the impact of dysbiosis on clinical outcomes and associations with secondary super-infections during critical illness have not been defined. We sought to examine the temporal evolution of respiratory and intestinal communities, their relatedness over time and associations with clinical outcomes.

**Methods:** We enrolled consecutive mechanically-ventilated patients with acute respiratory failure and performed serial sampling of the following body-site communities: oral (oral swabs), lung (endotracheal aspirates) and gut (rectal swabs or stool samples) at three time intervals (baseline: within 48hrs of intubation; middle: days 3-6; late: days 7-10). We extracted DNA and performed amplification and sequencing of the V4 region of the 16S rRNA gene with Illumina MiSeq. We compared results to microbial communities in oral washes and bronchoalveolar lavage samples from healthy subjects, and examined for associations of microbiome profiles with 30-day mortality and microbiologically-confirmed ventilator-associated pneumonia (VAP).

**Results:** 133 critically-ill patients (mean age 55 years, 56% men) yielded 563 microbiome samples for analysis. Compared to healthy controls, mechanically-ventilated patients had much lower alpha-diversity at baseline in their oral (mean Shannon[Standard Deviation]: 2.3[1.1] vs. 3.6[0.4], p=10-16) and lung communities (2.2[1.1] vs. 3.7[1.1], p=10-7). Despite low baseline values, alpha-diversity declined overtime in all three body-sites (mixed-effects regression p<0.05). Mortality was associated with lower oral community alpha-diversity in the late interval (p=0.009), with similar non-significant trends in lung and gut communities. Comparing beta-diversity, oral-lung communities were more similar than gut-lung communities at all time-intervals (p<0.05). Baseline composition of neither oral nor lung communities was predictive of subsequent VAP development. However, at the time of VAP diagnosis, significant differences were found both in the beta-diversity of oral and lung communities in patients with VAP (Permanova p-values<0.009), but not in the gut.

**Conclusion:** Our findings reveal a pattern of evolving dysbiosis of microbial communities across different body-sites in mechanically-ventilated patients, evidenced by global declines in alpha-diversity overtime. The high oral-lung taxonomic similarity and association with VAP development suggests that micro-aspiration of oral bacteria (rather than gut translocation) represents the main force shaping the respiratory tract community structure. Functional and mechanistic studies are needed to elucidate whether observed changes in microbiota are markers of illness severity or whether they play causal roles in critical illness evolution.
Introduction: Pseudomonas (P.) aeruginosa, an opportunistic Gram-negative bacterium, is the most common pathogen isolated in cystic fibrosis (CF) patients or patients with ventilation. P. aeruginosa infection leads to acute lung injury and acute respiratory distress syndrome that is a severe public health concern. The molecular mechanism(s) underlying is not fully studied. E3 ubiquitin ligases, catalyze a key step of protein ubiquitination, are exclusively involved in life processes including host defense against pathogen infection. The role of E3 ubiquitin ligases in P. aeruginosa infection remains unclear.

Methods: Molecular and cellular biological and biochemical approaches have been used to dissect the mechanism. These techniques include molecular cloning, qRT-PCR, western blotting, ci-precipitation, cell culture, bacterial infection, bacterial infection, siRNA, Crispr-Cas9 knockout, fluorescent immunostaining, and RNA sequencing. Human infected lung tissues, human primary lung epithelial cells, and animal models are also used to prove the hypothesis.

Results: P. aeruginosa infection increased an E3 ubiquitin ligase component Fbxo9 protein without substantial affecting its mRNA level in Beas-2B cells and primary human small airway epithelial cells. Fbxo9 was unstable and underwent ubiquitin proteasomal degradation mediated by E3 ligase SCF-Fbxw7. P. aeruginosa decreased Fbxw7 to stabilize and accumulate Fbxo9 in Beas-2B cells. Importantly, we identified that the protein level of Fbxo9 was positively correlated to the bacterial load in Beas-2B cells. Knock-down of Fbxo9 enhanced the clearance of intercellular P. aeruginosa which may partially through regulation the gene level of several cytokines including IL6, IFNgamma, and TGFbeta1 which are associated with host defense against microbial pathogens.

Conclusion: The protein stability of Fbxo9 is positively correlated to P. aeruginosa infection in lung epithelial cells that may pave new avenues against P. aeruginosa infection.
**Poster: Characterization of donor-specific alloreactive CD4+ and CD8+ cellular immune T cell responses in the lung allograft and blood in lung transplant recipients**

**Presenter:** Iulia Popescu, Junior Faculty

**Research Interest:** Translational

Pulmonary, Allergy and Critical Care Medicine

**Mentors:** John McDyer MD

**Funding Source:** ITTC

**Authors:** Iulia Popescu PhD, Carlo Iasella PharmD, Elizabeth Lendermon MD, Spencer Winters MD, John Sembrat BSc, Brianna Hewitt MBBS, Ritchie Koshy MBBS, Yingze Zhang PhD, Vera Iouchmanov MBBS, Mark Brown BSc, Bruce Johnson MD, Silpa Kilaru MD, Matthew Morrell MD, Joseph Pilewski MD, John McDyer MD

**Introduction:** Lung transplantation remains the only therapeutic option for select patients with end-stage lung diseases, however chronic lung allograft dysfunction (CLAD) significantly limits long-term survival in lung transplant recipients (LTRs). Episodes of acute cellular rejection (ACR) are common and the major risk factor for developing CLAD, however little is known about donor-specific cellular T cell responses, as these have not been previously characterized in LTRs.

**Methods:** We used a novel ex vivo flow cytometric assay to assess donor-specific alloimmune responses from LTRs cells in lung allograft resident effector T cells (BAL-derived) and PBMC. Using a 6h in vitro re-stimulation protocol with either irradiated donor cells or donor lysate, we measured the frequencies of effector responses (IFN-?, TNF-a, the cytotoxic marker CD107a, IL-17a, IL-13, IL-2 and the costimulation surface molecule, CD154) from CD4+ and CD8+ lung resident or blood compartment T cells.

**Results:** Overall the predominant alloreactive effector responses were donor-specific CD154 surface expression following in vitro re-stimulation with donor lysate in lung resident CD4+ T cells compared to the PBMC compartment, with minimal to absent expression on CD8+ T cells. Expression of surface CD154 was highly co-expressed with allospecific CD4+ T cells producing the Type-1 cytokines IFN-?, TNF-a and CD107a suggesting CD154 as a marker for Type-1 effector function, but not Type-2 or Type-17 responses. In fact, donor-specific IL-13 and IL-17 responses were detectable in some patients but at significantly lower frequencies compared to Type-1 effector responses, suggesting a hierarchy of alloeffect immune responses. Comparison between the lung resident T cells and blood T cells revealed consistently increased donor-specific alloreactive frequencies in the lung allograft versus the periphery. Ongoing experiments are assessing the proliferative capacities of donor-specific alloreactive T cell populations in the blood compartment.

**Conclusion:** Together, these data indicate donor-specific alloreactive effector CD4+CD154+ lung resident T cells activated via the indirect allorecognition pathway are present in high frequencies in LTRs with histologic evidence or history of ACR and segregate to Type-1 effector cytokine responses.
**Introduction:** Deprescribing, the systematic process of identifying and discontinuing medications, is an intervention to reverse the possible iatrogenic harms of potentially inappropriate or unnecessary medications. While literature has suggested these medications increase burden, there has been mixed evidence to support if a reduction in medication burden improves wellbeing. Therefore, we conducted this study to explore the impact of deprescribing on quality of life (QOL).

**Methods:** The protocol was listed on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42017078534. The Cochrane Library, Cumulative Index to Nursing and Allied Health (CINAHL), MEDLINE, and EMBASE were searched from database inception until November 2017. Two independent reviewers screened all retrieved articles for inclusion via Distiller SR, assessed study quality and extracted data. Eligible studies included those where older adults had at least one medication deprescribed versus usual care. The primary outcome was participant or designated representative self-reported change in QOL. Secondary outcomes were participant or designated representative self-reported satisfaction with care, and hospitalizations and emergency department visits. Risk of bias was assessed using measures recommended by the Cochrane Collaboration.

**Results:** Screening of 6,543 identified fifteen studies with a total of 1,923 participants. In twelve studies comparing the reduction of at least one medication deprescribed, compared to usual care, most found no difference in QOL. Only one randomized, multi-centered, pragmatic study in older adults with serious illness, who received a statin for 3 months or longer for both primary or secondary prevention, found total QOL to be significantly higher for patients in the statin discontinuation group. To date there has only been one study exploring the impact of deprescribing on patient satisfaction, which was found to be insignificant. Lastly, in the four studies exploring the impact of deprescribing on emergency room visits and rehospitalizations, again most found no difference. Only one non-randomized study of a single Geriatric Medical Center found the patients’ annual referral rate to acute care facilities was 30% in the control group but only 11.8% in the study group. Many studies were found to have a higher performance, detection or attrition bias. We found considerable heterogeneity in the populations and QOL measurements used in these studies, and that many utilized a placebo medication, instead of a reduction in number of medications, in the intervention groups.

**Conclusion:** Based on a limited number of studies with varying methodological rigor, our results suggest deprescribing does not significantly impact QOL. Future controlled studies are needed.
Poster: SCUBE1: A Novel Pathogenic Effector in Pulmonary Endothelium and Potential Clinical Marker in Pulmonary Arterial Hypertension

Presenter: Wei Sun, Clinical Fellow

Research Interest: Translational Cardiology

Mentors: Stephen Chan MD PhD

Funding Source: T32

Authors: Wei Sun MD, Adam Handen MSc, Gil Speyer PhD, Seungchan Kim PhD, Yingze Zhang PhD, Marc Simon MD, Annie Watson MD, Yassmin Al Aaraj MD, John Sembrat, Mauricio Rojas, Stephen Chan MD PhD

Introduction: Pulmonary arterial hypertension (PAH) is a highly morbid disease characterized by progressive remodeling of the pulmonary vasculature, increased pulmonary pressures and right heart failure. Current therapies for PAH do not stop or reverse the disease, largely due to poorly defined molecular origins of this disease. Previously, we re-analyzed the reported RNA-Seq data generated from iPSC-derived endothelial cells from individuals carrying pathogenic BMPR2 mutations predisposing to heritable PAH. Signal Peptide CUB-EGF-Domain Containing Protein 1 (SCUBE1), a membrane protein with unique molecular structure with BMP1 domain, was found to be differentially expressed under BMPR2 mutation. Given the potential interaction with BMPR2 signaling, we considered SCUBE1 as a compelling candidate that may play a pathogenic role in PAH.

Methods: The expression of SCUBE1 in human pulmonary arterial endothelial cells (PAECs) was evaluated with RT-PCR and immunoblotting. Angiogenesis potential of PAECs was quantified with Matrigel tube formation. Plasma samples were collected from 46 PAH patients and 35 non-PAH controls. Rapid autopsy or transplant lung tissues were derived from 8 PAH patients and 11 non-PAH controls. SCUBE1 in PAEC culture medium, patient plasma, and lung tissue was measured by ELISA. Clinical characteristics and right heart catheterization measurements in PAH patients were analyzed to identify correlations with SCUBE1 levels.

Results: SCUBE1 was expressed substantially in PAECs but was undetectable in smooth muscle, suggesting an endothelial-specific expression in pulmonary vasculature. BMPR2 knockdown or hypoxia treatments in PAECs controlled SCUBE1 expression in biphasic manner: upregulation acutely followed by downregulation more chronically, suggesting a complex regulatory mechanism for SCUBE1. SCUBE1 knockdown in PAECs significantly inhibited tube formation in Matrigel by 24%, suggesting a pro-angiogenic function of SCUBE1. SCUBE1 levels in plasma and lung tissues from PAH patients were significantly lower than non-PAH controls (median 5.3ng/ml vs 2.1ng/ml in plasma, 6.9ng/mg tissue vs 4.7ng/mg tissue in lungs). The plasma SCUBE1 level in PAH patients were negatively correlated to mean PA pressure, PVR and RV function, suggesting plasma SCUBE1 as a potential clinical marker reflecting the severity and progression of PAH.

Conclusion: SCUBE1 is a secreted endothelial-specific protein that is controlled by acquired and genetic triggers of PAH and modulates angiogenic activity. In PAH patients, SCUBE1 levels in plasma and lung tissues are decreased and negatively correlated to the severity of disease. These results support the notion that SCUBE1 may act as an important effector involved in pathogenic endothelial alterations in PAH and could serve as a useful clinical marker in PAH patients for diagnosis and monitoring of disease progression.
128-A  **Poster:** Single-cell analysis reveals fibroblast heterogeneity and myofibroblasts in systemic sclerosis-associated interstitial lung disease

**Presenter:** Eleanor Valenzi, Post-Doctoral Scholar

**Research Interest:** Translational

Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Robert Lafyatis MD

**Funding Source:** T32

**Authors:** Eleanor Valenzi MD, Melissa Bulik BS, Tracy Tabib MS, Christina Morse BS, John Sembrat MS, Humberto Trejo Bittar MD, Mauricio Rojas MD, Robert Lafyatis MD

**Introduction:** Interstitial lung disease is a leading cause of disease-related mortality in patients with systemic sclerosis (SSc). Myofibroblasts are key effector cells in the extracellular matrix remodeling of systemic sclerosis-associated interstitial lung disease (SSc-ILD), with previous studies relying on smooth muscle actin staining to identify these cells due to a lack of more specific markers. We sought to define the transcriptome map of myofibroblasts and other mesenchymal cell populations in human SSc-ILD and healthy control lungs to understand how alterations in fibroblast phenotypes lead to SSc-ILD.

**Methods:** We performed droplet-based single-cell RNA-sequencing (scRNA-seq) with integrated canonical correlation analysis of 13 explanted lung tissue specimens (56,196 cells post-filtering) from 4 healthy control and 4 SSc-ILD patients, with immunohistochemical and immunofluorescence confirmation of the identified myofibroblast population.

**Results:** Examination of gene expression in mesenchymal cells identified two major, SPINT2hi and MFAP5hi, and one minor, WIF1hi, fibroblast subpopulation in the healthy control lung. Combined analysis of control and SSc-ILD mesenchymal cells identified SPINT2hi, MFAP5hi, and few WIF1hi fibroblasts, as well as a new large myofibroblast population with 3.21-fold increased expression of ACTA2 compared to the other fibroblast populations in the SSc-ILD lung. There was evidence of actively proliferating myofibroblasts in the SSc-ILD lung. Comparing differential gene expression of all fibroblasts from SSc-ILD to controls, 461 genes were up-regulated and 155 genes were down-regulated by greater than twofold, with many of the non-collagen up-regulated genes including POSTN, COMP, ADAM12, and MXRA5 distinctly present in the myofibroblasts. The myofibroblasts also expressed the highest COL1A1, COL1A2, and COL3A1, amongst other collagens. The population of smooth muscle cells and pericytes increased significantly in SSc-ILD upper lobes compared to healthy control lungs (p-value=0.0209), with FAM162B identified as a more specific marker of the pericyte population than other markers previously published.

**Conclusion:** Our results demonstrate that previously unrecognized fibroblast heterogeneity exists in SSc-ILD and healthy lungs, and define transcriptome-phenotypes associated with these populations, thus identifying new specific markers of myofibroblast, fibroblast, and pericyte populations. Our data indicate that myofibroblast differentiation and proliferation are key pathologic mechanisms driving fibrosis in SSc-ILD.
129-A  Poster: Combined Airway Transcriptome Analysis and Immune Proteome Profiling of the Lung Allograft Identifies a Type-1 Immune Signature and Indoleamine 2,3-dioxygenase 1 (IDO1) as a Potential Biomarker of Chronic Lung Allograft Dysfunction.

Presenter: Jianxin Wei, Research Associate

Research Interest: Translational
Pulmonary, Allergy and Critical Care Medicine

Mentors: John McDyer MD

Funding Source: Cystic Fibrosis Foundation

Authors: Jianxin Wei MS, Aki Hoji PhD, Carlo Iasella PhD, Annabel Ferguson PhD, Naveen Jain BS, Yingze Zhang PhD, Mark Brown BS, Elizabeth Lendermon MD, Bruce Johnson MD, Sílpa Kilaru MD, Joseph Pilewski MD, Matthew Morrell MD, Wei Chen MD, Kong Chen PhD, John McDyer MD

Introduction: Chronic lung allograft dysfunction (CLAD) is the major limitation to long-term survival of lung transplant recipients (LTRs) and the underlying biologic mechanisms that drive CLAD remain poorly understood. To discover biomarker candidate genes and address molecular pathogenesis of CLAD, we performed transcriptome analysis of airway brush samples in conjunction with Meso Scale Discovery (MSD) multiplex cytokine and chemokine measurements in human bronchial lavage (BAL) samples.

Methods: Total RNA from human distal bronchial brush samples and 28-day post transplant mouse allografts (F1 B6/DBA>DBA) and isografts (DBA>DBA) were sequenced using an Illumina instrument to obtain bulk RNA-seq data. These data were subsequently analyzed for the top differentially expressed genes (DEGs) controlling for potential batch effect and using false discovery rate (FDR) p<0.05 as a cutoff value. Gene enrichment analyses were used to predict canonical pathways and activated upstream signal pathways. Immune proteome profiles of BAL from corresponding LTRs were analyzed by multiplex MSD array. Quantitative PCR (qPCR) and western blot analysis of mouse IDO1 were also performed.

Results: 21 CLAD and 18 control LTRs were used in the RNA-seq analysis of airway brushes. The top DEGs included IDO1 (p<1.78E-14) and TNFRSF6B (p<1E-16), both of which are checkpoint molecules known to be up-regulated by a Type-1 immune response. Ingenuity Pathway Analysis revealed IFN-α (p<7.07E-45), TNF-α (p<1.09E-41) and IL-1β (p<5.24E-40) among the top activated pathways, supporting both a Type-1 immune response and inflammasome molecular signatures in human CLAD. Concurrent MSD analysis of BAL supernatants also demonstrated significant increases in levels of the Type 1 cytokines IL-12/IL-23p40 (p<0.01), TNF-a (p<0.007) and the inflammasome component, IL-1β (p<0.03) in CLAD LTRs compared to stable control LTRs. Next, we studied chronic allograft rejection in the mouse orthotopic lung transplant model. We performed RNA-seq analysis in 3 mice with obliterative airways disease (F1>DBA) and 3 isograft controls (DBA>DBA) at day 28. Transcriptome analyses showed striking up-regulation of mouse ido1 in OAD allografts (p<1E-16). Subsequent western blot and qPCR analyses in mouse lung allografts with OAD at day 28 confirmed the transcriptomic analyses.

Conclusion: Our study shows that CLAD is associated with activation of type 1 immune responses and the inflammasome and implicates IDO1 as a potential biomarker common to human CLAD and mouse OAD. Further analyses will elucidate the immune role of IDO1 in CLAD and potentially uncover distinct immune endotypes within CLAD.
130-A  **Poster:** Protective ventilation of donor after cardiac death extends warm ischemic tolerance of lung grafts to 4 hours

**Presenter:** Che Xu, Graduate Student

**Research Interest:** Translational
                  Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Xingan Wang PhD

**Funding Source:** CMRF2018

**Authors:** Che Xu MD, Junyi Yu MD, Xingan Wang PhD

**Introduction:** Donation after cardiac death (DCD) is supposed to enlarge donor pool. However, the maximum of warm ischemia (WI) is only 2h. Uniquely, lungs can get oxygen directly from alveoli after circulatory arrest. We hypothesized that oxygen supply would enhance the WI tolerance of DCD lungs.

**Methods:** To study WI without oxygen deficit, the left pulmonary artery (PAC) in B6 mice was ligated for 4h or 5h, followed by 24h reperfusion. Then the reperfusion injury induced by WI with or without oxygen deficit were investigated in a mouse model of lung transplantation. Before lung retrieval, the donor mice were subjected to PAC for 4h (PAC4-LTx), overdosed and ventilated at 37ºC with a protective strategy for 4h (37V4-LTx) or overdosed and left no touch at 37ºC for 4h (37N4-LTx).

**Results:** The lung function and histology were almost normal in “4h PAC+24 R” but markedly impaired in “5h PAC+24 R”. The grafts in 37N4-LTx developed severe necrosis, hemorrhage and infiltration after reperfusion. With oxygen supply during WI, 37V4-LTx and PAC4-LTx represented less graft injury, infiltration, local and systemic inflammatory response and the activation of intrinsic apoptosis. Consistently, the ATP levels dropped markedly at the end of WI in 37N4-LTx but not in the other two.

**Conclusion:** Mouse lungs can tolerate up to 4h WI at 37 ºC. Protective ventilation is effective to protect DCD lungs against ATP depletion.
**Introduction:** Immunosuppression, also called “immunoparalysis”, is characterized by suppressed immune responses to infection and to tumors, including a reduced population of immune cells, exhaustion and dysfunction of cell immunity, release of anti-inflammatory factors, or suppression of pro-inflammatory factor secretion. Immunosuppression has been typically emphasized in cancers, in chronic viral infections, and in acute infectious illness such as sepsis. An initial hyperactive immune response shifting to immunosuppression renders a poor prognosis in ALI/ARDS patients. Epigenetics modulates innate immunity via multiple channels and is believed to be crucial in immunosuppression. However, the role of epigenetics in septic ALI/ARDS pathophysiology linked to immunosuppression is an under investigated area of study.

**Methods:** Molecular and cellular biological and biochemical approaches including cloning, site directed mutagenesis, lentiviral small hairpin RNA knockdown, Crispr-Cas9 knockout techniques, RNA sequencing, subcellular protein fraction, confocal microscopy, and fluorescent immunostaining were used in the study. We used LPS lung injury and LPS-Pseudomonas aeruginosa two-hit lung injury murine models to validate the function of Gcn5l2 in immunosuppression. We used human infected lung tissue samples to test our fundamental hypotheses to understand Gcn5l2 epigenetic roles in the pathogenesis of human disease.

**Results:** We show here that a major protein acetyltransferase Gcn5l2 (general control of amino acid synthesis protein 5-like 2) was elevated at protein levels in human infected lung tissues and in LPS treated lung epithelial cells without remarkable alteration in mRNA levels. Gcn5l2 was unstable (t1/2 ~ 4 h) degraded by the ubiquitin proteasome system on chromatin via an E3 ubiquitin ligase called SCF-Fbxo24. LPS stabilized Gcn5l2 by relocation of nuclear Fbxo24 to the cytoplasmic compartment. Elevated Gcn5l2 repressed pro-inflammatory gene transcription by inhibition of epigenetic transcriptional markers in a LPS-tolerance model (24 h). Knockout (KO) of Gcn5l2 by Crispr-Cas9 techniques reversed, in part, LPS-suppressed pro-inflammatory gene transcription. Inhibition of Gcn5l2 with small molecule promoted gene transcription in immunosuppression mouse models.

**Conclusion:** These findings indicate that elevated Gcn5l2 suppressed active transcriptional epigenetic markers to silence gene transcription thereby causing reduced innate immune responses in a negative feedback loop that led to immunosuppression in acute lung injury models.
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1-B Poster: Defective fatty acid metabolism in lung epithelial cells leads to senescence

Presenter: Diana Álvarez, Post-Doctoral Associate

Research Interest: Bench (Basic Science)
Aging Institute

Mentors: Ana L Mora MD

Funding Source: NIH, Aging Institute and VMI U Pitt, ITM & HCWP

Authors: Diana Álvarez MD, Lan Tu MD, Marta Bueno PhD, Christian Baker BS, John Sembrat MSc, Tracy Tabib MS, Steven Mullett MS, Stacy Wendell PhD, Claudette St. Croix PhD, Sruti Shiva PhD, Robert Lafyatis MD, Eric Goetzman PhD, Mauricio Rojas MD, Ana L Mora MD

Introduction: Idiopathic Pulmonary Fibrosis (IPF) is a fatal aged-related disease of unknown etiology characterized by lung scarring and decreased lung function. As an age-related disease, senescence has been implicated as an important pathogenic process in lung fibrosis. Cellular senescence can be induced by a number of stressors including mitochondrial dysfunction. We have previously found accumulation of dysfunctional mitochondria in type II lung epithelial cells (AECII) from IPF lungs. The potential role of mitochondrial alterations in the senescence phenotype in IPF is unknown.

Methods: Single cell RNA sequencing (scRNAseq) and metabolic analysis were performed in lungs from control donors and IPF explanted lungs. Expression of key metabolic genes and markers of senescence were validated in tissue and isolated primary AECII by qRT-PCR, immunoblot and immunofluorescence assays. In parallel, mouse lung epithelial cells (MLE) were used for in vitro studies.

Results: AECII from IPF lungs showed significant decrease in transcript and protein levels of genes involved in fatty acid oxidation (FAO), including CPT1a, the limiting enzyme in FAO. Metabolomics data confirmed the defective FAO and showed low levels of acetyl-CoA in IPF lungs. CPT1a knockdown in MLE cells was correlated with defective mitochondrial respiration and decrease in the levels of acetyl-CoA, hypoacetylation of histone proteins, and elevated expression of markers of senescence including SA-β-Galactosidase, p53, p21, as well as the presence of a senescence associated secretory phenotype.

Conclusion: Our study provides novel mechanistic insights connecting aging, mitochondria dysfunction, and dysregulated FA metabolism as driving forces for cellular senescence. AECII are essential to promote re-epithelization and repair, and their increase in senescence might contribute to aberrant repair and fibrosis. Manipulating alveolar epithelial cell metabolism by restoring FAO pathway could be a novel therapeutic approach against lung fibrosis.
**Introduction:** The blood brain barrier (BBB), a structure composed of blood vessels, endothelial cells (EC), astrocytes, pericytes, and other cells, protects the brain against harmful substances but also prevents the passage of many therapeutics. Ultrasound Targeted Microbubble Cavitation (UTMC) has been shown to transiently open the BBB without neuronal tissue damage, but its mechanisms of action are not fully understood.

**Methods:** An in vitro BBB model featuring a transwell support system with a microporous, collagen IV/fibronectin coated membrane bathed in culture medium allowed the growth of two individual cell layers. The bottom was seeded with C57-BL/6 mouse brain EC's while the top was either seeded with mouse astrocytes or no cells. The system was exposed to pulsed ultrasound (1 MHz, 250 kPa pressure, 10 µs pulse duration, 10 ms pulse interval) for 20 seconds after microbubbles and FITC-Dextran (10 kD, 100 µg/mL) were added to the bottom well (US+MB). The concentration of FITC-Dextran in the top well was measured at various times post US treatment as a permeability marker. Transwells with no cells (Blank), transwells receiving no ultrasound (no US), and transwells with ultrasound treatment but without microbubbles (US only) served as controls. After 180 minutes, propidium iodide (PI) and Hoechst stains were performed, assessing cell viability and coverage respectively. Data were presented as mean ± SD with unpaired two-tailed t-tests.

**Results:** Monolayer FITC-Dextran concentrations at 180 min showed no significant difference between the no US (n=9) and US only (n=7) groups (p=0.18). UTMC treatment group (US+MB, n=9) showed significantly higher FITC-Dextran concentrations compared with no US and US only groups (p<0.001 for both). Bilayer FITC-Dextran concentrations at 180 min showed no significant differences between the no US (n=9), US only (n=9), and US+MB (n=9) groups. The no US, US only, and US+MB groups in the monolayer compared to the bilayer all showed significantly lower concentrations in the bilayer compared to the monolayer (p=0.003, p<0.001, and p<0.001 respectively). Hoechst and PI staining confirmed high cell coverage and low cell death respectively in every model group.

**Conclusion:** UTMC increased endothelial barrier permeability in the monolayer model. The bilayer model was less prone to UTMC-induced hyperpermeability but was also less permeable overall, more closely recapitulating the physiologic barrier function of the BBB. Future studies will include more sensitive indices of endothelial barrier permeability such as transendothelial electrical resistance measurements. Additional acoustic parameters will be investigated for their effects on permeability.
**Poster:** Development of C-C Chemokine Receptor 2 (CCR2) Antagonists for Theranostics

**Presenter:** Michael Bellavia, Graduate Student

**Research Interest:** Bench (Basic Science)  
Cardiology Affiliated

**Mentors:** Carolyn Anderson PhD

**Funding Source:** R01

**Authors:** Michael Bellavia MS, Philip Mannes BS, Carolyn Anderson PhD

**Introduction:** C-C chemokine receptor type 2 (CCR2) is a G protein-coupled receptor expressed on immune cells, namely monocytes and macrophages, that prompts the migration of these immune cells to areas of inflammation upon binding one of its endogenous ligands, usually C-C chemokine ligand 2 (CCL2). Given this role, the CCL2-CCR2 axis is implicated in a broad array of pathologies marked by chronic inflammation, such as cancer, tuberculosis, atherosclerosis, and neuropathic pain among others. As such, there has been extensive development of small molecule CCR2 antagonists, yet none have shown clinical efficacy. Others have pioneered and demonstrated the therapeutic benefit of the peptide CCR2 antagonist ECL1i in animal models, yet ECL1i suffers from rapid blood clearance, undermining its theranostic potential.

**Methods:** Here we introduce a novel small molecule orthosteric CCR2 antagonist and compare its binding metrics (Ki, IC50) to those of ECL1i via radioligand binding assays involving 125I-labeled recombinant human CCL2. Binding was evaluated in model overexpression systems for both mouse and human CCR2.

**Results:** The small molecule inhibitor was successfully synthesized, as verified by mass spectroscopy (MS) and nuclear magnetic resonance spectroscopy (NMR). ECL1i was synthesized by standard Fmoc solid phase peptide chemistry, as confirmed by MS. ECL1i has been further modified for the conjugation of radionuclide chelators.

**Conclusion:** Insights gained will guide further development of both the small molecule antagonist and ECL1i towards use as imaging agents suitable for positron emission tomography (PET) imaging of disease, and possibly as inhibitors of CCR2 to block monocyte/macrophage migration in cancer.
**4-B Poster:** Nrf2 interactions with the HIF system may determine long term outcomes after acute kidney injury

**Presenter:** Corry Bondi, Post-Doctoral Scholar

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Roderick Tan MD

**Funding Source:** T32

**Authors:** Corry Bondi PhD, Brittney Rush BS, Roderick Tan MD

**Introduction:** Acute kidney injury (AKI) affects up to 1 in 5 hospitalized patients and is associated with an increased risk of developing chronic kidney disease. AKI is commonly caused by ischemia and proximal tubular epithelia are particularly vulnerable to injury. HIF-1α (Hypoxia-inducible factor-1α) and Nrf2 (Nuclear factor erythroid 2-related factor 2) are transcription factors with protective effects against AKI. Studies suggest an association between HIF system activation and Nrf2 activity but this has not been extensively studied in the kidney.

**Methods:** C57Bl/6 mice were subjected to kidney ischemia-reperfusion to induce AKI. Ischemia times were titrated to induce mild to severe injury and kidneys were harvested at various acute and chronic timepoints post-reperfusion. To simulate mild and severe injury conditions in vitro, proximal tubular HK-2 cells were exposed to either nutrient replete or nutrient deficient conditions, respectively, in the presence of HIF activation with cobalt chloride (CoCl2). Immunoblotting, qPCR, RNA interference, serum creatinine, and histologic methods were used.

**Results:** Kidneys obtained 24 h after mild injury had elevated protective Nrf2 activity, as evidenced by expression of the Nrf2 target gene Nqo1, and this was associated with minimal histologic injury at late timepoints. Kidneys exposed to severe injury failed to upregulate Nqo1, and this was associated with the development of chronic injury and fibrosis. Similarly, HK-2 cells exposed to mild stress conditions using nutrient replete media with CoCl2 led to Nqo1 upregulation, but cells exposed to nutrient deficient conditions with CoCl2 did not show Nqo1 induction. HIF-1α appeared to exert a negative effect on Nrf2 since HIF-1α knockdown enhanced Nqo1 expression. HIF-1α activation also suppressed Nrf2 nuclear localization in nutrient deficient conditions.

**Conclusion:** Our data suggest there is a threshold of severity at which AKI leads to the development of progressive CKD, and disparate outcomes may be partly determined by Nrf2 activity. Also, we demonstrate differential regulation of Nrf2 by HIF activation in mild and severe injury conditions. Overall, our results show that there is an association between Nrf2 and the HIF system that may determine the long-term outcome of the kidney.
**Poster: The Effects of Dietary Potassium on Mouse Blood Pressure and Ion Transport**

**Presenter:** Cary Boyd-Shiwarski, Junior Faculty

**Research Interest:** Bench (Basic Science)
Renal-Electrolyte

**Mentors:** Arohan Subramanya MD

**Funding Source:** K08

**Authors:** Cary Boyd-Shiwarski MD, Rebecca Beacham BS, Claire Weaver Undergrad, Lubika Nkashama BS, Daniel Shiwarski PhD, Stephanie Mutchler BS, Kelly Connolly BS, Allison Marciszyn PhD, Arohan Subramanya MD

**Introduction:** For almost a century it has been appreciated that in humans, dietary potassium intake correlates inversely with blood pressure. Yet, it is unclear how potassium restriction leads to hypertension, and how potassium excess causes a natriuresis despite elevated aldosterone levels. Our goal was to study the effects of dietary potassium in a wild-type SV129 mouse model to determine the role of K+ in blood pressure, volume regulation, acid/base balance, and ion transport.

**Methods:** Mice were fed 4 different diets: low K+, normal K+, high K+ alkali, and high KCl diet for 10 days. Results were obtained using radiotelemetry probes, metabolic cages, and western blots. We found that simply restricting K+ intake had no effect on blood pressure, whereas potassium loading resulted in a progressive ~10 mmHg increase in blood pressure over the 10d feeding period. To determine whether these effects were dependent on NaCl intake, we challenged mice with 1% saline, added to their drinking water.

**Results:** The K+ restricted mice developed a rapid NaCl-induced increase in blood pressure (~8 mmHg), whereas potassium loaded mice exhibited no significant change in blood pressure with saline supplementation. Notably, even a limited K+ restricted period of 10d was associated with the development of nephrogenic DI in this model, evidenced by polyuria and a decrease in AQP2 expression. This was associated with an increase in the expression of sodium transporters in the proximal tubule and distal convoluted tubule, likely the cause of salt sensitivity. The elevated blood pressure on the K+ supplemented diet was consistent with an effect on transport in the aldosterone-sensitive distal nephron, and correlated with elevated aldosterone levels, increased activation-associated cleavage of ENaC, and was amiloride-sensitive. During K+ loading, despite no differences of dietary anionic content on blood pressure, the expression of NHE3 in proximal tubule and pendrin in intercalated cells were differentially regulated by basic and chloride-rich diets.

**Conclusion:** Collectively, these findings suggest that in our mouse model, the effect of dietary K+ on blood pressure is linked to NaCl intake, due to differential effects of K+ loading and restriction on sodium transport pathways along the entire length of the nephron. In conclusion, standard mouse diets that simply modulate K+ content do not recapitulate the previously reported effects of dietary potassium on blood pressure in humans. Rather, the dietary sodium:potassium ratio as well as the accompanying anionic content should be taken into consideration when modeling the physiologic effect of K+ intake on tubular salt transport and blood pressure.
**Poster:** Increased cellular senescence in CF lung cells can be reverted by B-MSC conditioned media

**Presenter:** Nayra Cardenes, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Mauricio Rojas MD

**Funding Source:** RO1

**Authors:** Nayra Cardenes PhD, Hesper Wong BS, Jordan Bullock BS, Elisa Heidrich MS, Michael Myerburg MD, John Sembrat BS, Nathaniel Weathington MD, Mauricio Rojas MD

**Introduction:** The cystic fibrosis transmembrane conductance regulator (CFTR) protein is a complex molecule that functions as a chloride channel. Mutations in this gene result in loss of chloride conductance across epithelial cells and in the clinical disease cystic fibrosis (CF). The unfolded mutated protein CFTR-?F508, often accounting for this pathology, is retained in the endoplasmic reticulum (ER) and induces stress that has been reported to be activated in senescent cells. Cellular senescence is a permanent state of cell cycle arrest accompanied by resistance to apoptosis and production of a bioactive secretome known as the senescence-associated secretory phenotype (SASP), which results in chronic inflammation. Senescence is activated upon cellular damage as a defense mechanism, participating in multiple pathologies, therefore, exocrine senescence has been proposed as a mechanism in chronic lung diseases. Furthermore, increased expression of senescence markers has been shown in cystic fibrosis airways, and a proinflammatory environment has been shown to decrease CFTR expression and function in airway epithelial cells.

**Methods:** Conditioned Media (CM) from bone marrow-derived mesenchymal stem cells (B-MSC) was used for culture of CF human bronchial epithelial cells (HBE) or CF human lung fibroblasts (hLF). Expression of CFTR and senescence markers was measured by qRT-PCR. CFTR expression was also quantified by WB.

**Results:** We aimed to examine if lung cells of CF patients presented increased expression of senescence markers and if such phenotype could be reverted. MSC and their CM have been widely used for their anti-inflammatory properties as therapy. We used CM from B-MSC to modify the senescence phenotype of primary CF HBE and hLF. CF samples showed an increase in senescence in whole lung tissue, HBE and hLF. When treated with B-MSC CM from young, healthy donors, there was a robust 30% reduction in expression of p16INK4A in HBE, whereas in hLF reduction of senescence appeared to be targeted through the p21-p53 pathway. Additionally, the expression of CFTR was restored in CF HBE when treated with B-MSC CM. This presents a promising therapy to restore CFTR activity in the cell.

**Conclusion:** The vast majority of clinical trials have focused on CFTR replacement therapy. The transfer of wt CFTR to CF cells mediated by extracellular vesicles (EVs) has shown restoration of CFTR function in CF recipient cells. The possibility of the transfer of CFTR from B-MSC via EV-containing CM into CF HBE and hLF presents as an attractive alternative with additional important therapeutic effects, such as anti-inflammatory and anti-senescence consequences.
7-B  **Poster:** Characterization of Putative Promoters of Relaxin/Insulin-Like Family Peptide Receptor 1 in Idiopathic Pulmonary Fibrosis Fibroblasts

**Presenter:** Ting-Yun Chen, Graduate Student

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Yingze Zhang PhD

**Funding Source:** R21 and NIH

**Authors:** Ting-Yun Chen MS, Jiangning Tan PhD, Ching-Hsia Hung PhD, Daniel Totten PhD, Harinath Bahudhanapati PhD, Tin-Kan Hung PhD, Daniel Kass PhD, Yingze Zhang PhD

**Introduction:** Disease progression in idiopathic pulmonary fibrosis (IPF) is irreversible and no effective treatment is currently available. In a relaxin knockout mouse model, spontaneous development of age related tissue fibrosis can be reversed by restoring relaxin levels. Relaxin is a peptide hormone that can loose collagen fiber and help collagen fiber breakdown in fibrotic tissues. Relaxin is a potential therapeutic target for pulmonary fibrosis. However, no antifibrotic effect in scleroderma patients with treatment of recombinant relaxin was observed. Recently, we have found decreased levels of Relaxin/insulin-like family peptide receptor 1 (RXFP1), the relaxin receptor, in IPF patients. The lower expression levels of RXFP1 may represent a potential limitation for relaxin-based therapies in IPF patients. Upregulation of RXFP1 expression in IPF patients is essential for relaxin-based therapy. We hypothesized that aberrant transcriptional regulation may lead to RXFP1 down-regulation in IPF. The goal of our study is to characterize the RXFP1 gene regulation in fibroblasts.

**Methods:** The genomic structure of the regulatory region of RXFP1 gene locus, was determined using UCSC browser and Berkeley Drosophila Genome Project. Two regions had been designated as proximal promoter (pp) and distal premotor (dp) according to the differential transcripts with different length recorded in the GENCODE database. We have cloned 3.1 kb and 1.4 kb of dp and pp to the pGL3 system and analyzed the promoter and enhancer activity of these putative promoters using firefly luciferase assay.

**Results:** In the preliminary analysis, both promoters had minimum promoter activity in pGL3basic systems using primary lung fibroblasts. However, we observed dramatic enhancer activity for the dp region when it was cloned into pGL3promoter system. This enhancer activity is much more profound in lung fibroblasts isolated from donor lungs than IPF fibroblasts (138 fold vs 57 fold). Fine mapping of the cis-acting enhancer elements and transcription factors are on-going.

**Conclusion:** Two putative promoter regions separated by 204.4 kb DNA sequences have differential enhancer activity in donor and IPF lung fibroblasts. Further characterization of these regions and other regulatory regions in both normal and IPF lung fibroblasts will provide insight into the aberrant expression of RXFP1 in IPF patients and may lead to new therapeutic targets.
8-B  **Poster:** ATF3 pleiotropic functions over IPF lung fibroblast

**Presenter:** Tamara Cruz, Post-Doctoral Fellow

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Mauricio Rojas MD

**Funding Source:** R01 HL123766

**Authors:** Tamara Cruz PhD, Diana Alvarez MD, John Sembrat, Jordan Bullock BS, Marta Bueno PhD, Nayra Cardenes PhD, Ana Mora MD, Mauricio Rojas MD

**Introduction:** Endoplasmic reticulum (ER) stress is associated with the development and progression of fibrotic diseases, including idiopathic pulmonary fibrosis (IPF). However, the pathway by which ER stress induces senescence associated fibrosis remains unknown. Activating transcription factor (ATF-3) has been described as an integral player between the Unfolded Protein Response (UPR) and the effector pathways during ER stress response. In this study, our objectives are to determine the pathways compromised by activated ATF3 during ER stress response.

**Methods:** Lung fibroblasts were isolated from explanted IPF lungs and age-matched normal lungs not suitable for transplant. Normal and IPF lung fibroblast were cultured in the presence of tunicamycin (5 mg/ml for 24h, 48h and 72h to induce ER stress). Changes in gene and protein expression were determined by qRT-PCR and western blot, respectively. Tunicamycin-induced apoptosis was quantified by TUNEL assay and senescence by β-Gal staining.

**Results:** After tunicamycin, we observed similar activation of the UPR in normal and IPF fibroblasts. However, we observed that only IPF fibroblasts have an increase in the expression of cell cycle inhibitors p21cip, p53 and SASPs fibronectin. No differences in expression were observed on normal donors. Increased markers of senescence were associated with overexpression of the full length and the truncated isoforms. CCAAT/Enhancer-Binding Protein Homologous Protein (CHOP) was also overexpressed, as well as some Apoptotic IPF lung fibroblast.

**Conclusion:** Our data suggests that ER stress alone is not enough for the induction of cell senescence in human lung fibroblast. But in primed cells with accumulation of DNA damage or oxidative stress, tunicamycin is able to drive the cell into senescence and apoptosis. We propose that ER stress-induced overexpression of ATF3 can have pleiotropic functions over susceptible cells.
9-B  Poster: Expression and Distribution of PIEZO1 in the mouse urinary tract

Presenter: Marianela Dalghi, Post-Doctoral Associate

Research Interest: Bench (Basic Science)  
Renal-Electrolyte

Mentors: Gerard Apodaca PhD

Funding Source: Urology Care Foundation Research Scholar Award

Authors: Marianela Dalghi PhD, Dennis Clayton, Wily Ruiz, Mohammad Al-bataineh PhD, Lisa Satlin MD, Thomas Kleyman MD, William Ricke PhD, Marcelo Carattino PhD, Gerard Apodaca PhD

Introduction: Sensing and responding to mechanical forces including shear stress and wall tension are critical for the proper function of the urinary tract. The kidney must adjust water and solute flux in accordance with the rates of tubular flow, and the bladder must convey its filling status to the central nervous system to ensure normal voiding. Yet, we have limited understanding of the mechanosensors that function in these organs as well as their cell-type specific expression and subcellular distribution. Attractive candidates for mechanosensation in the urinary system include the stretch-activated PIEZO channels, which are directly gated by membrane tension and have been implicated in many other mechanically regulated body functions including touch sensation, proprioception, lung inflation, and blood pressure regulation.

Methods: A transgenic reporter mouse line that expresses the PIEZO1 channel fused at its C-terminal domain to the fluorescent tandem-dimer Tomato moiety (PIEZO1-tdT) was used to study the expression of Piezo1 in the urinary tract. PIEZO1 expression was assessed by SDS-PAGE and western blotting and tissue distribution and subcellular localization by immunofluorescence. All experiments were performed with females and males between 9- and 24-weeks old (N=3).

Results: We observed PIEZO1-tdT protein expression in lysates prepared from kidneys, ureter, bladder and urethra, with the following rank order: kidney > urethra > bladder > ureter. We next characterized the localization of PIEZO1-tdT within the urinary tract. In the kidney PIEZO1-tdT localizes to the renal corpuscle and basolateral surfaces of epithelial cells that line the distal nephron, collecting ducts, and renal pelvis. In the bladder and ureters PIEZO1-tdT is associated with the urothelium, interstitial cells, smooth muscle cells and mesothelium. PIEZO1-tdT is also expressed in the urethra and associated organs of female (vagina) and male (prostate) mice. In the vagina of the female mice, PIEZO1tdT was localized to all cell layers of the epithelium, and in the male PIEZO1-tdT is found in the prostate glands, seminal vesicles and ejaculatory ducts. In both, PIEZO1-tdT is strongly expressed in the stratified epithelium lining the urethra, where it as localized to the basolateral surface of the superficial cells and the surfaces of the underlying cell layers.

Conclusion: PIEZO1-tdT is expressed in all of the organs that comprise the upper and lower urinary tracts where it is associated with a diversity of cell types. We hypothesize that PIEZO1 is functioning as a channel-type mechanosensor in the urinary tract, likely playing a role in sensing changes in wall tension.
**Poster: Interleukin-22 controls RSV production in primary human airway epithelial cells**

**Presenter:** Sudipta Das, Research Scientist

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Prabir Ray PhD

**Authors:** Sudipta Das PhD, Jay Kolls MD, Anuradha Ray PhD, Prabir Ray PhD

**Introduction:** Respiratory syncytial virus (RSV) infection can cause severe bronchiolitis and pneumonia in infants, often requiring hospitalization. It is one of the major causes of morbidity and mortality in early life worldwide. However, for some infant’s RSV infection causes milder symptoms while in others it can be life-threatening. RSV primarily infects lung epithelial cells which includes both proximal and distal airways as well as alveolar epithelial cells. Currently, no effective vaccine is available against RSV infection. Therefore, alternate strategies are needed to defend against this common pathogen. The cytokine interleukin-22 (IL-22) has mucosal-protective effects known to preserve epithelial-barrier functions and promote host defense against pathogens. We, therefore, initiated studies to determine whether IL-22 can control RSV infection in primary human airway epithelial cells and in vivo in a mouse model of infection.

**Methods:** Primary human airway epithelial cells (AECs) were grown under air-liquid interface (ALI) culture conditions for 14 days for differentiation. The cells were then infected with RSV and at 2h post-infection (p.i.) cells were treated or not with IL-22 (50 ng/ml) at a multiplicity of infection (MOI) of 2. Cells were collected at 24 and 48h post infection (p.i.) and viral load and mRNA expression for various interferon stimulated genes (ISGs) were assessed. To address the effect of IL-22 in a neonatal mouse model, 5-day old C57BL/6 mice were intranasally infected with 1×106 PFU of RSV and then treated with an IL-22-Fc fusion protein (5 µg/mouse) intraperitoneally on day 3 p.i. Viral load in the lung was assayed on day 6 p.i.

**Results:** Treatment with IL-22 resulted in a significant decrease in viral load in primary human AECs. However, this decrease in viral load was not associated with differential infection as confirmed by similar levels of RSV-L-polymerase mRNA expression. The anti-viral effect of IL-22 was also found not to be regulated by expression of different interferon stimulated genes (ISG) in the primary epithelial cells. IL-22-Fc treatment of RSV-infected mice significantly reduced viral load in the lungs demonstrating anti-viral effect of IL-22 in vivo as well.

**Conclusion:** Decreased viral load in both primary human airway epithelial cells and mouse lungs after IL-22 treatment shows anti-viral effects of IL-22 against RSV. Ongoing work is devoted to understanding the mechanism underlying this process. Collectively, the results of our study suggest that IL-22 has therapeutic benefit during RSV infection.
Poster: Tissue Plasminogen Activator (tPA) loaded Microbubbles for the Treatment of Coronary Microvascular Obstruction

Presenter: Stephen D'Auria, Clinical Fellow

Research Interest: Bench (Basic Science) Cardiology

Mentors: John Pacella MD

Funding Source: HVI Fellows Research Grant

Authors: Stephen D'Auria MD, Gary Yu, Filip Istvanic, Francois Yu PhD, Tapas Nayak PhD, Xucai Chen PhD, John Pacella MD

Introduction: Microvascular obstruction (MVO) occurs frequently during successful PCI for acute myocardial infarction (AMI). MVO limits myocardial salvage and is the primary contributor to post AMI congestive heart failure. Our previous work demonstrated that using ultrasound targeted microbubble cavitation (UTMC) relieves MVO, termed sonoreperfusion (SRP). In the present study, we sought to develop tPA loaded MBs to further enhance the efficacy of SRP through targeted delivery of tPA.

Methods: tPA loaded MBs were created, first by linking tPA to biotin, using either BMCC-biotin or NHS-PEG4-Biotin. The biotinylated tPA was then mixed with streptavidin labeled lipid shelled MBs via biotin-streptavidin bridging. The enzymatic activity of the tPA in these tPA loaded MBs was tested with whole porcine blood thrombus and with a tPA chromogenic activity kit. The loading capability of tPA onto the MBs was determined by BCA protein assay. The SRP efficacy of the loaded tPA MB was tested in an in vitro model of MVO and compared with full dose systemic tPA.

Results: tPA activity was preserved and was similar between stock tPA and the tPA conjugated MB using both linker molecules. tPA loaded MBs showed successful lysis of whole porcine blood clot in vitro, as evidenced by decreased thrombus weight. The loading capability of tPA onto the MBs using the two linker molecules was 10%. In our in vitro model of MVO, the reperfusion efficacy of the tPA loaded MBs utilizing the NHS-PEG4-Biotin linker was noninferior to full systemic dose tPA, but at a fraction of the tPA dose.

Conclusion: We successfully loaded tPA onto the surface of lipid encapsulated MBs, with full preservation of the enzymatic lytic activity of tPA. These tPA loaded MBs were noninferior to full systemic dose tPA at relieving MVO in our in vitro model, but at a fraction of the systemic tPA dose. This strategy of targeted MB delivery of tPA provides an opportunity to further enhance SRP efficacy, while minimizing potential bleeding risks associated with systemic dose tPA.
Poster Abstracts

12-B Poster: Nox1/Ref-1-Mediated Activation of CREB Promotes Gremlin1-Driven Endothelial Cell Proliferation

Presenter: Daniel de Jesus, Post-Doctoral Fellow

Research Interest: Bench (Basic Science)

VMI

Mentors: Patrick Pagano PhD

Funding Source: AHA Postdoctoral Fellowship

Authors: Daniel de Jesus PhD, Evan DeVallance PhD, Yao Li PhD, Micol Fallabela PhD, Danielle Guimaraes PhD, Patrick Pagano PhD

Introduction: Pulmonary arterial hypertension (PAH) is a complex and progressive disorder, characterized by an increase in vascular remodeling, a rise in pulmonary arterial pressure and right heart failure. Recently, we and others showed that BMP antagonist Gremlin1 elicits pulmonary endothelial cell (EC) proliferation in response to hypoxia and that Gremlin1 haploinsufficiency attenuates PAH. NADPH oxidase (Nox)-derived reactive oxygen species (ROS) seem to play a pivotal role in PAH. However, the mechanisms by which ROS propagates the disease are unclear. Transcription factor CREB, which is activated by hypoxia, ROS, and interaction with Ref-1 (redox factor 1), mediates gene transcription related to proliferation and vascular remodeling. We postulated that Nox1/Ref-1-mediated CREB activation leads to Gremlin1-induced EC proliferation.

Methods: Human pulmonary arterial EC (HPAECs, Lonza) were subjected to 24 hr hypoxia (1% O2 vs. normoxia - 21% O2) to mimic the EC phenotype in PAH. Western Blotting was used for protein expression, CBA probe for hydrogen peroxide production, flow cytometry for cell cycle progression, crystal violet for cell proliferation, confocal for CREB/Ref-1 interaction, ELISA assay for CREB:CRE binding, and Co-IP for CREB/Ref-1 binding.

Results: Hypoxia upregulated Nox1 protein level (1.40±0.09-fold, p<0.05) and H2O2 production level/mg protein (2.20±0.21-fold, p<0.0001) vs. normoxia. siNox1 (Nox1 gene silencing) abolished hypoxia-induced Nox1, and Nox1 inhibitor, NoxA1ds, decreased hypoxia-promoted H2O2. Moreover, siNox1 decreased hypoxia-induced pCREB (1.74±0.22-fold v. normoxia, vs. 1.07±0.08 siNox1+hypoxia, p<0.05), and siCREB decreased hypoxia-induced Gremlin1 (1.83±0.16 hypoxia vs. 0.35±0.01 siCREB+hypoxia, p<0.05). Further, hypoxia augmented nuclear pCREB/Ref-1 interaction (1.812±0.207-fold vs. normoxia, p<0.05) and pCREB association with its DNA binding motif. siRNA for Ref-1 impaired hypoxia-induced pCREB DNA binding (1.96±0.06 hypoxia vs. 0.815±0.219 siRef-1+hypoxia, p<0.01). Moreover, siCREB decreased hypoxia-induced EC proliferation (1.40±0.050 hypoxia vs. 0.96±0.04 siCREB+hypoxia). Finally, preliminary data show pCREB binding to the Gremlin1 promoter.

Conclusion: Taken together, our data support a previously unidentified redox signaling pathway by which Nox1-derived ROS promote Gremlin1 expression and EC proliferation in PAH.
**Introduction:** Pulmonary arterial hypertension (PAH) is a devastating disease with 7-year survival under 50%. A common feature of PAH is vascular remodeling mediated by altered bone morphogenetic protein receptor 2 (BMPR2) signaling. Our lab previously demonstrated that hypoxic injury to human pulmonary endothelial cells (hPAEC) characteristically recapitulates PAH and activates Nox1-mediated BMPR2 antagonist, Gremlin1 (Grem1), promoting hPAEC proliferation. However, the mechanism by which Grem1 mediates hPAEC proliferation is unknown. CXC Motif Chemokine Ligand 12 (CXCL12) signaling induces a number of pathways mediating cell migration, proliferation, and metabolism. Recently, increased CXCL12 expression was shown in PAH lungs. However, the mechanisms of CXCL12 upregulation and signaling pathways in hPAEC remain poorly understood. BMPR2-SMAD4 signaling is suggested to repress CXCL12 in other cell types. Thus, BMPR2 antagonism by Grem1 could mediate elevations in CXCL12. We hypothesize that hypoxia-induced Grem1 de-represses CXCL12 in hPAECs; and, in turn, elevated CXCL12 mediates hPAEC glucose 6-phosphate dehydrogenase (G6PD) activity, proliferation, and migration.

**Methods:** Ex-planted lung lysates obtained from non-PAH and PAH patients were probed with anti-CXCL12 antibody (ab9797). Cultured hPAEC from Lonza were utilized between passage 3-6 exposed to normoxic (21%) or hypoxic (1%) conditions for 24 and 48 hours with siRNA silencing of SMAD4 and CXCL12. Samples were assessed by PCR, western blot, and enzymatic activity assays.

**Results:** Lysates of lungs from PAH vs. non-PAH human subjects tended to display increases in CXCL12 protein expression. In vitro, hPAEC exposed to 48 hr of hypoxia (1% O2) showed a trend toward an increased CXCL12 expression (2.8 ± 0.8-fold, p=0.06) vs. normoxia (21% O2). Twenty-four hour treatment with 100 ng CXCL12 increased G6PD activity (2.1±0.3 vs. 1.3±0.2 ng/ml/min, p<0.05), and proliferation (1.7±0.1-fold, p<0.05). In contrast, silencing CXCL12 under hypoxic conditions reduced G6PD activity (0.75±0.1 v. 1.6±0.1 ng/ml/min, p<0.05). To investigate potential BMPR2 repression of CXCL12, we exposed normoxic hPAECs to SMAD4 siRNA, which increased CXCL12 1.6±0.1-fold (n=6, p<0.05). Wound-healing assay showed SMAD4 siRNA under normoxic conditions increased wound closure, which was blunted by co-transfection with CXCL12 siRNA.

**Conclusion:** These results suggest a clinically relevant mechanism by which PAH and hypoxia leads to Grem1 antagonizing the SMAD4 repression of CXCL12. In turn, CXCL12 signaling appears to cause hPAEC proliferation via upregulation of essential metabolic pathways.
Introduction: Hypertension is a major risk factor for cardiovascular-related morbidity and mortality. Nitric oxide (NO) resistance results in an inability of arterial blood vessels to relax contributing to hypertension. NO relaxes vascular smooth muscle cells (SMCs) by stimulating soluble guanylyl cyclase (sGC) to generate cyclic guanosine monophosphate (cGMP) which leads to downstream activation of protein kinase G (PKG) and vasodilation. This signaling cascade requires the sGC heme be in the reduced (Fe2+) state in order for NO to bind and activate sGC. When sGC becomes heme-deficient or oxidized (Fe3+) in response to oxidative stress, sGC is rendered insensitive to NO resulting in increased vasoconstriction and hypertension. We recently published evidence that NADH cytochrome b5 reductase 3 (CYB5R3) is a sGC heme reductase that maintains sGC in the reduced (Fe2+), NO sensitive state. We hypothesized that CYB5R3 in SMCs would influence systemic blood pressure by maintaining sGC in its reduced heme state.

Methods: To test this, we created tamoxifen-inducible SMC-specific Cyb5r3 knockout mice (SMC CYB5R3 KO). Measurements of vessel function by ex-vivo two-pin myography and blood pressure were conducted in WT and SMC CYB5R3 KO mice in non-diseased conditions and in the context of Angiotensin-II induced hypertension.

Results: We discovered non-diseased SMC CYB5R3 KO mice have a significant 6.2 mmHg higher mean arterial pressure as compared to WT controls (n=10 per group). Additionally, this difference in mean arterial pressure is further increased to a peak 17.3 mmHg difference after 7 days of Angiotensin II (Ang II) - induced hypertensive treatment (n=8-10 per group). Ex-vivo myography experiments (n=8-12 per group) assessing vessel function in resistance mesenteric arteries from 14 day Ang II-treated mice showed that SMC CYB5R3 KO mice have an impaired vasodilation response to NO-donor sodium nitroprusside compared to WT mice. SMC CYB5R3 KO mice also have an enhanced vasodilation response to BAY 58-2272, an sGC activator drug that acts on oxidized or heme-deficient sGC to induces vasodilation, compared to WT controls. Lastly, intraperitoneal injections delivering acute doses of BAY 58-2667 in Ang II-treated mice showed that SMC CYB5R3 KO mice mean arterial pressure significantly decreased and thus were more responsive to vasodilator BAY 58-2667 than WT controls (n=4 per group).

Conclusion: Taken together, the data provide evidence that SMC CYB5R3 can regulate systemic blood pressure and confers protection against Ang II-induced hypertension by maintaining sGC in the reduced (Fe2+), NO sensitive state.
15-B Poster: Liver-specific deletion of the mitochondrial quality control E3 ligase PARKIN is associated with increased hepatic steatosis and markers of NAFLD in diet-induced obese mice.

Presenter: Lia Edmunds, Post-Doctoral Scholar

Research Interest: Bench (Basic Science) Endocrinology and Metabolism

Mentors: Michael Jurczak PhD

Funding Source: ADA Postdoctoral Fellowship

Authors: Lia Edmunds PhD, Amanda Mills BS, Michael Jurczak PhD

Introduction: PARKIN, an ubiquitin E3 ligase, regulates mitochondrial homeostasis through a process called mitophagy, where damaged mitochondria are selectively targeted and removed via autophagy. Diminished hepatic mitophagy may play a role in mitochondrial dysfunction that occurs alongside insulin resistance and steatosis in association with obesity. Reduced hepatic mitophagy was observed in obese mice with fatty liver, raising the question as to whether loss of mitophagy contributes to the pathogenesis of fatty liver or is merely associated with the disease.

Methods: To understand how loss of hepatic mitophagy affects obesity-associated liver disease, we developed a liver-specific PARKIN knockout mouse (LKO). There was no difference in body weight in LKO compared with WT mice fed regular chow (RC) or high-fat diet (HFD; 60% kcal, 12 weeks).

Results: There was also no difference in liver steatosis between RC groups, however, liver steatosis was 45% greater in HFD-LKO compared with WT mice (p<0.05). Liver histology demonstrated presence of microvesicular steatosis in zones 2-3 in both HFD groups, but only LKO mice presented with micro and macrosteatosis in zones 1-3. HFD-LKO samples showed presence of an inflammatory cell infiltrate that was less apparent in WT samples. Unbiased transcriptomic analysis by RNA-Seq demonstrated 113 significant differentially expressed genes (82 up, 31 down) in HFD-LKO mice. Unsupervised gene ontology and pathway analysis revealed significant changes in extracellular matrix accumulation, lipid metabolism, metabolic and ROS processes in HFD-LKO mice.

Conclusion: In summary, the increased steatosis and presence of macrovesicular steatosis and inflammation in HFD-LKO mice, alongside changes in gene expression suggesting collagen deposition and extracellular matrix remodeling, suggest that loss of PARKIN-mediated mitophagy increases susceptibility to HFD and may predispose mice to NAFLD.

**Presenter:** Mitra Eghbal, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)  
Infectious Diseases

**Mentors:** Matthew Culyba MD PhD

**Funding Source:** University of Pittsburgh

**Authors:** Mitra Eghbal PhD, Tejas Paranjpe MPH, Ryan Shields PharmD MS, Matthew Culyba MD PhD

**Introduction:** Methicillin-resistant Staphylococcus aureus (MRSA) is a pathogen of global significance that poses significant challenges in clinical treatment. In this study, we sought to expand our understanding of MRSA's evolutionary trajectory within patients undergoing treatment for infection. Antibiotics used in patient treatment included daptomycin and vancomycin. Extensive intra-patient sampling of MRSA isolates and subsequent genomic sequencing and fitness assays of the isolates allowed us a close examination of existing diversity within the infecting MRSA populations. We describe our continual efforts to link genotype with phenotype in the isolates, with the ultimate goal of uncovering novel targets relevant to clinical treatment.

**Methods:** A total of 78 MRSA samples were isolated across five different patients undergoing treatment for persistent bloodstream infection (BSI). The patients ranged in age from 37-75. Each patient's blood was sampled for culture across multiple time points (between 8-13 time points per patient, over a span of 9-22 days) during the course of routine clinical care. Genomic DNA was extracted from each harvested isolate. The whole genomes of each isolate were sequenced with Illumina NextSeq with a mean coverage greater than 50x. For the growth assays, the isolates were inoculated into Mueller Hinton broth in 96-well plates and their density in a shaking Tecan plate reader was recorded over a period of 13 hours.

**Results:** Growth curves suggest significant variation in relative fitness across isolates, even within isolates that were harvested from the same patient. Isolates from one patient had polymorphism at two different loci within the relA gene (a known mediator of the stringent response in bacteria); the same patient's isolates also had polymorphism for citZ (known to be involved in biofilm formation). In other patients' isolates, nonconservative mutations were also detected in rpoB (known to be involved in rifampicin resistance) and tcaR (known to be involved in teicoplanin resistance), among other genes. There was also marked polymorphism in genes of as-yet-unknown function.

**Conclusion:** Extensive intra-patient variation in phenotype and genotype were detected: variability in growth rates, and gene polymorphism, including within genes known to be involved in resistance and virulence. Variants in the gene relA may be associated with significantly diminished growth rate.
17-B Poster: Age-related Cardiac Amyloidosis: Structure-Toxicity Relationships in an Underdiagnosed, but Increasingly Prevalent Disorder

Presenter: Yvonne Eisele, Junior Faculty

Research Interest: Bench (Basic Science) Cardiology

Funding Source: NIA K99/R00

Authors: Genevieve Doyon BSc, Mandy Janssen PhD, Dan Ma BSc, Bianca Nguyen BSc, Lars Plate PhD, Gareth Morgan PhD, Natalia Reixach PhD, Joel Buxbaum PhD, R. Luke Wiseman PhD, Gabriel Lander PhD, Jeffery W. Kelly PhD, Prem Soman MD, Yvonne S. Eisele PhD

Introduction: Older age is often associated with irreversible protein aggregation and amyloid formation. Depending on the protein involved, this leads to devastating diseases like Alzheimer's disease or Parkinson's disease that affect the brain, or may affect other organs like the peripheral nervous system or the heart. Transthyretin (TTR) amyloidosis is an increasingly prevalent but difficult to diagnose disorder that presents with peripheral polyneuropathy, cardiomyopathy, and/or cerebral amyloid angiopathy. We identified and characterized previously unrecognized, non-native TTR aggregates in patient samples that might explain the degenerative phenotype.

Methods: Blood plasma of patients with familial and sporadic forms of TTR amyloidosis were screened for the presence of non-native TTR aggregates utilizing newly developed antibodies. TTR aggregate formation was also modeled in vitro and electron microscopy (EM) was used to delineate a structural model. Stability and cytotoxicity of disease-associated TTR aggregates was assessed.

Results: High molecular weight TTR aggregates are present in plasma of patients with a predominantly polyneuropathy phenotype of TTR amyloidosis, but absent in healthy controls. TTR aggregate formation is accompanied by a loss of protein function and a gain of cytotoxicity. Atomic force microscopy and EM reveal distinct rod-like structures, albeit with some heterogeneity. Interestingly, this aggregate type is not readily detectable in the cardiomyopathy subtype of the disease. We are currently investigating the TTR aggregate species that drive the cardiac phenotype.

Conclusion: The observed presence, stability and cytotoxicity of TTR oligomers suggests that circulating TTR oligomers in blood plasma of patients with systemic TTR amyloidosis might be an important contributor linking TTR aggregation to cytotoxicity and tissue degeneration. Disease phenotype and organ tropism may be governed by differences in protein aggregate conformation. Delineating structure-toxicity relationships in amyloid disorders is the new frontier and will allow us to refine diagnosis and well as therapeutic approaches.
**18-B Poster:** Distinct plasma gradients of microRNA-204 in the pulmonary circulation of patients suffering from World Health Organization Groups I and II pulmonary hypertension

**Presenter:** Leonard Estephan, Research II

**Research Interest:** Bench (Basic Science)  
VMI

**Mentors:** Stephen Chan MD PhD

**Authors:** Leonard Estephan BS, Michael Genuardi MD, Chad Kosanovich MD, Michael Risbano MD, Anjali Vaidya MD, Akaya Smith MD, Jeremy Mazurek MD, Yuchi Han MD, Stephen Chan MD PhD

**Introduction:** Pulmonary hypertension (PH) is an enigmatic vascular disease classified into five groups/subtypes by the World Health Organization. Group II PH can mimic Group I PH, thus complicating diagnosis and clinical management. Thus, identification of molecular markers unique to each PH subtype could have substantial translational importance. Circulating microRNAs (c-miRNAs) in plasma, molecules that negatively regulate gene expression, have been proposed as potential biomarkers in PH. Namely, muscle-specific miR-204 is known to be down-regulated in diseased pulmonary vasculature, but its regulation in plasma across PH subtypes has not been studied. Distinct differences in c-miRNA expression profiles of Group I vs. Group II PH patients could reveal novel molecular manifestations, contributing to further differentiation of PH classifications.

**Methods:** Patients (n=91) from two designated PH Comprehensive Care Centers at UPMC and the University of Pennsylvania were clinically classified as Group I PH (n=47), Group II PH (n=22), or non-diseased (n=22). Via right heart catheterization, blood was drawn across three serial anatomic sites in the pulmonary circulation (right atrium, pulmonary artery, and pulmonary vascular wedge) within each patient, followed by plasma RNA extraction. Using reverse transcription-quantitative polymerase chain reaction (RT-qPCR), levels of PH-associated and muscle-enriched c-miRNAs were quantified.

**Results:** c-miR-204 displayed a dynamic up-regulation across the pulmonary vascular bed of Group I PH (log fold change slope = 0.22 [95% CI 0.06, 0.37], p=0.008). Such up-regulation was not observed in Group II PH and non-diseased individuals, nor was it observed for a separate muscle-specific miRNA, c-miR-208. A receiver operating characteristic curve was utilized to quantify whether these alterations of c-miR-204 could potentially discriminate Group I vs. II PH, resulting in an area under the curve (AUC) of 0.72.

**Conclusion:** A stepwise gradient of c-miR-204 expression across the pulmonary vascular bed reveals a novel and differentiating molecular manifestation specific to Group I but not Group II PH. Future studies across a larger cohort of PH patients are necessary to determine the utility of c-miR-204 as a biomarker for these deadly disease subtypes.
**Introduction:** Cognitive impairment and neurodegenerative disorders are increasingly prevalent in an aging population. Aging also affects sleep, which is critical for restoring brain energy, impacting learning and memory, and aiding in neurotoxin removal. However, the relationship between neurodegeneration and sleep with increasing age is not well understood and clinically-confounded by the presence of multiple co-morbidities. Thus, our goal was to investigate changes in sleep patterns and neurodegeneration over the lifespan in a model of recessive Parkinson's Disease using PINK1 knockout (KO) mice.

**Methods:** PINK1 KO mice and wild type (WT) littermates were studied at three age ranges: early adulthood (4.5-5.5 months, EA), middle adulthood (8.5-10 months, MA) and late adulthood (13-14.5 months, LA). Mice underwent electroencephalographic (EEG) and nuchal electromyographic (EMG) electrode implantation and, after tethering and acclimation, sleep was recorded for two consecutive days. After the baseline sleep study, a subset of animals from each age group underwent a sleep fragmentation (SF) protocol for two consecutive days: using an automated feedback system, a high-pressure air blast was initiated to induce an awakening whenever $=30$ seconds of sleep was detected. For the SF protocol, data were combined across age groups. Histological staining was used to objectively characterize neurodegeneration of sleep areas.

**Results:** Independent of strain, we found a trend for a decrease in awake time with increasing age (EA: 48.8±2.0, MA: 44.7±1.6 and LA: 43.7±0.8 % awake/24h; p=0.09) and a comparable trend for an increase in time in NREM sleep with increasing age; there was no effect of age on time in REM sleep. Furthermore, we did not observe any independent effect of the KO strain on awake time or time spent in NREM and REM sleep. However, WT mice spent more time awake during the SF protocol (WT: 61.1±1.7, KO: 57.7±1.7 % awake/24h; p<0.01) despite a similar number of air blasts/24h (WT: 975±153, KO: 1016±155; n.s.). Air blasts were of longer duration in KO animals (WT: 12.0±1.8, KO: 17.7±5.1 sec; p<0.01).

**Conclusion:** We determined there is a tendency for an increase in NREM sleep time across the lifespan that was unaltered by knockout of the PINK1 gene. However, the absence of PINK1 signaling did increase the threshold for arousal from sleep.
**Poster:** Heterogeneity in Multi-organ Expression of HO-1 and PlGF in Sickle Mice Mimic Exposure of Non-sickle Mice to Extracellular Heme via Nrf2-Dependent Pathways

**Presenter:** Oluwabukola Gbotosho, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)
  VMI

**Mentors:** Gregory Kato MD

**Funding Source:** HLBVMI

**Authors:** Maria Kapetanaki PhD, Samit Ghosh PhD, Yu Lin , Frances Weidert MSc, Solomon Ofori-Acquah PhD, Gregory Kato MD

**Introduction:** Hemolysis is a major feature of sickle cell disease (SCD) that contributes to organ damage. Release of free heme, a byproduct of hemolysis, into the circulation causes damage to multiple organs in patients with SCD. Heme oxygenase-1 (HO-1) is the rate-limiting enzyme for the degradation of heme from damaged or senescent red blood cells, conferring an antioxidant and anti-inflammatory cytoprotective effect. Conversely, Placental Growth Factor (PlGF) promotes vasculopathy and inflammation in SCD. Here, we assessed organ-specific response to heme induction of PlGF and HO-1, as a way to identify organs most at risk in SCD during acute elevation of circulating extracellular heme.

**Methods:** Mouse experiments: Mice were infused with hemin (120µMol/Kg bodyweight) for 3 hours, followed by detection of PIgF, HMOX-1 and Hrg1 in the organs. Real time qPCR: Transcripts were quantified using Taqman Gene Expression Assays from ABI. Relative expression changes were calculated with the DeltaDeltaCt method. Heme quantification: Total heme in perfused organ lysates was quantified using a colorimetric assay kit (Bioassay Systems) and total protein in the lysates with BCA assay kit.

**Results:** In adult Townes sickle (SS) mice, we found significant (p<0.0001) organ variability in basal mRNA expression of both HO-1 and PlGF. Moreover, intravenous injection of exogenous heme prominently induced HO-1 and PlGF transcripts in the heart. The SS basal expression pattern is largely reproduced in C57BL/6J wild type mice by heme injection, especially in the heart. While the Nuclear factor (erythroid derived 2)-like 2 (Nrf2) transcription factor was required for maximal heme induction of HO-1 and the heme transporter Hrg1 in all organs, we observed organ-specific differences in the degree of Nrf2-dependence for both of these markers. Interestingly, after heme injection, the heme content of all organs was highly correlated with induction of HO-1 (R^2=0.82, p=0.03) and heme transporter Hrg1 (R^2=0.82, p=0.004).

**Conclusion:** Our findings support the idea of organ-specific differential effects of SCD-associated hemolysis, which may promote organ-specific protective and maladaptive responses that contribute to the pattern of organ damage in SCD patients.
**21-B Poster:** A beta-chain derivative of human relaxin-2 rescues mouse bladders with irradiation-induced cystitis

**Presenter:** Samuel Getchell, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Anthony Kanai PhD

**Funding Source:** NIH R01/P01, DOD

**Authors:** Samuel Getchell PhD, Irina Zabbarova PhD, Youko Ikeda PhD, Mark Kozlowski BS, Amanda Wolf-Johnston BA, Lori Birder PhD, Anthony Kanai PhD

**Introduction:** Radiation cystitis is a consequence of radiotherapy for pelvic malignancies. Acutely, irradiation leads to reactive oxygen/nitrogen species in urothelial cells, apoptosis, barrier disruption, and inflammation. Chronically, this results in collagen deposition, bladder fibrosis, and attenuated storage and voiding functions. In severe cases, cystectomies may be necessary as currently approved therapies do not reverse fibrosis. In previous studies, we demonstrated the benefits of human relaxin-2 (hRLX2) in treating radiation cystitis. However, as hRLX2 is angiogenic and may be contraindicated in those with malignancies, we investigated the therapeutic potential of a single-chain peptide derivative (B7-33) of hRLX2 in reversing radiation-induced bladder fibrosis and the accompanying lower urinary tract dysfunction.

**Methods:** We performed cell-based assays for relaxin receptor type-1 (RXFP1)-dependent formation of cyclic adenosine monophosphate (cAMP) which mediates angiogenesis and compared the effects of B7-33 to the native ligand hRLX2. RXFP1 is the receptor most sensitive to hRLX2. The effects of B7-33 peptide were also functionally assessed in our mouse model of chronic radiation cystitis, where bladders are selectively irradiated (10 Gray) and develop extensive fibrosis by 6 weeks post-exposure. Accordingly, seven weeks post-irradiation, female C57Bl/6 mice were continuously infused with B7-33 (400 µg/kg/day/14 days) or vehicle (saline) via subcutaneous osmotic pumps. Mice were evaluated in vivo using urine spot analysis, cystometrograms and external urethral sphincter electromyograms, and in vitro using bladder sheet length-tension measurements.

**Results:** In HEK-293T cells transfected with human RXFP1, B7-33 induced formation of cAMP, though B7-33 required concentrations roughly 100-fold higher than hRLX2 for similar effects. However, in irradiated mouse bladders, B7-33 was therapeutic at a similar concentration to hRLX2 and lowered basal bladder pressure and increased voiding intercontractile intervals and bladder compliance, effects known to be mediated through the cGMP pathway. Treatment outcomes were likely due to activation of the related receptors RXFP1 and RXFP2 which are both expressed in the detrusor.

**Conclusion:** B7-33 may be a new therapeutic option for rescuing bladders in patients with chronic radiation cystitis. B7-33 offers advantages over hRLX2 in that it is less likely to induce angiogenesis, making it safer to use in patients undergoing radiotherapy for pelvic cancers. As hRLX2 can activate both RXFP1 and RXFP2, future investigations will seek to determine the relative contributions of these receptors in treating bladder dysfunction.
**22-B Poster:** Hemoglobin selectively inhibits renal proximal tubular uptake of proteins: Implications for vitamin D deficiency and kidney disease in sickle cell disease

**Presenter:** Megan Gliozzi, Graduate Student

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Ora Weisz PhD

**Funding Source:** T32

**Authors:** Megan Gliozzi BS, Youssef Rbaibi BS, Dario Vitturi PhD, Jesús Tejero PhD

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**Introduction:** Proximal tubule (PT) dysfunction, including tubular proteinuria, is a common early symptom of kidney disease in sickle cell disease (SCD) patients and can eventually lead to chronic kidney disease. PT dysfunction in SCD is thought to be caused by exposure to higher cell-free hemoglobin (Hb) concentrations from increased red blood cell hemolysis. This Hb enters the tubule lumen, where it is reabsorbed by PT cells upon binding to multiligand receptors megalin and cubilin. Megalin and cubilin bind to numerous proteins in the kidney filtrate, including albumin, vitamin D binding protein (DBP), and retinol binding protein (RBP), and are important for maintaining a protein-free urine and for vitamin homeostasis. We previously found that Hb impairs uptake of albumin by PT cells via direct megalin/cubilin binding competition. In this study, we further evaluate the consequences of increased Hb concentrations on PT vitamin D reabsorption and activation.

**Methods:** We treated PT cells with physiologic levels of Hb estimated in SCD and measured protein endocytosis and oxidative stress. Endocytosis of fluorescently-tagged DBP and RBP were quantified by confocal imaging and spectrofluorometry. Oxidative stress was assessed by measuring aconitase activity.

**Results:** We found PT cell DBP uptake was significantly inhibited by concentrations of Hb estimated to be filtered into the tubule lumen under chronic conditions (0.6µM Hb; 39% inhibition) and hemolytic crisis (~20µM Hb; up to 92% inhibition) in SCD patients. However, RBP uptake was minimally affected by the same Hb concentrations that profoundly inhibited DBP internalization. Mitochondrial oxidative stress, measured as a decrease in aconitase activity, was significantly increased in cells exposed to Hb (~43% and ~11% aconitase activity reduction after 72h 20µM Hb and 1µM Hb treatment, respectively).

**Conclusion:** Our results suggest that competition for megalin/cubilin binding between Hb and normally-filtered proteins, including DBP, may be the primary cause of tubular proteinuria in SCD patients. This inhibition appears to be selective for proteins that are largely a-helical in structure, such as albumin and DBP. Understanding the structural basis for Hb competition with filtered proteins for PT uptake could identify biomarkers to detect tubular proteinuria in SCD patients prior to the onset of kidney disease. This may also help develop therapeutic compounds that would selectively inhibit Hb binding to megalin/cubilin receptors. Additionally, inhibition of DBP uptake and vitamin D metabolism in the PT could lead or contribute to vitamin D deficiency. Ongoing studies focus on measuring vitamin D metabolism in both cell and mouse models of SCD.
**Poster Abstracts**

23-B **Poster:** Novel telemetry recordings from the urinary bladder and external urethral sphincter in awake freely moving mice

**Presenter:** Youko Ikeda, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Anthony Kanai PhD

**Funding Source:** NIH/NIDDK and DoD

**Authors:** Youko Ikeda PhD, Irina Zabbarova PhD, Samuel Getchell PhD, Mark Kozlowski BSc, Amanda Wolf-Johnston MSc, Lori Birder PhD, Anthony Kanai PhD

**Introduction:** There have been a variety of methodologies developed to obtain functional recordings from the lower urinary tract (LUT) of animal models. These include intravesical pressure recordings from the bladder and electromyograms from the external urethral sphincter (EUS). Simultaneous recordings from both structures are essential to obtaining a clear indication of voiding and storage functions. However, this necessitates the use of either anesthesia which dampen CNS reflexes, restraints which are accompanied by motion artifact or decerebration which does not require anesthesia but removes CNS influence. We have developed a method to record bladder and EUS activity in awake mice utilizing implantable telemeters combined with a metabolic cage system with custom load cells fitted with filter paper to measure urine void volumes, flow rates and spot patterns.

**Methods:** Adult (8-12 weeks) female and male C57Bl/6 mice were anesthetized and, under sterile conditions, a lower midline incision was made to expose the urinary bladder and proximal/mid urethra. An HDX-11 telemeter (Data Sciences International) was adapted to allow for implantation of a pressure catheter via the bladder dome and insertion of recording electrodes (50 micron stainless steel wire) into the EUS muscle. Telemeter sending units were placed subcutaneously on the flank of the animal and mice were allowed to recover with prophylactic analgesic and antibiotics. For recordings, mice were placed in the metabolic cages (Columbus Instruments) with the data from the telemeters and load cells recorded using LabChart 8 (ADInstruments).

**Results:** Bladder pressure and EUS electrical activity were recorded from both female and male mice (N=3 each). Micturition contractions indicated by a sharp rise in bladder pressure, were correlated with decreased tonic firing of the EUS indicating relaxation of the sphincter muscle. These events were followed by the measurement of urine flow rates and volumes, after a 0.5-1 second time delay for the urine to reach the load cells. Voiding patterns were measured using filter paper mounted on the load cells.

**Conclusion:** We have successfully recorded simultaneous bladder and EUS activity in awake freely moving mice. Our methodology has the added advantage of giving an accurate measurement of voided volumes, rates of voiding and voiding pattern. This technique has the potential for long-term monitoring of LUT function to better characterize pathologies or determine efficacy of treatments.
**Poster Abstracts**

**24-B Poster:** Metabolic reprogramming of neutrophils protects against bloodstream fungal infection in kidney dysfunction

**Presenter:** Chetan Jawale, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)  
Rheumatology and Clinical Immunology

**Mentors:** Partha Biswas PhD

**Funding Source:** NIH R01

**Authors:** Chetan Jawale PhD, Kritika Ramani PhD, Bianca Coleman MS, Sarah Gaffen PhD, Thomas Nolin PhD, Partha Biswas PhD

**Introduction:** Infections are the major cause of mortality (~20%) in patients with kidney disease, especially those on hemodialysis. Disseminated candidiasis (DC) caused by the fungus Candida albicans accounts for 79% of all systemic infections in patients with renal disease. Accumulation of uremic toxins in the absence of kidney function, also termed as uremia, is considered as an independent risk factor for infectious complications. However, the mechanisms by which uremia impacts antifungal immunity are unexplored.

**Methods:** Kidney disease was induced by injecting mice with Aristolochic acid-I, a nephrotoxin that causes renal fibrosis (AAI, 10 mg/kg body weight). At day 4 post AAI injection, mice were systemically infected with 1x10^5 CFU of C. albicans. Fungal burden from the organs was assessed by plating tissue homogenates on YPD agar. Bone marrow derived neutrophils were cultured with 50% control or uremic serum and assessed for phagocytosis, apoptosis and fungicidal activity. Neutrophil infiltration in the infected organs, ROS production, glucose uptake, glycolytic flux and intracellular cell signaling events were determined by flow cytometry, immunoblotting and biochemical assays.

**Results:** We show that uremic (AAI injected) mice are far more susceptible to DC than control animals. Neutrophils from uremic mice exhibit deficits in glucose uptake due to a defect in the expression of Glucose transporter 1 (Glut1). Neutrophils rely on glycolysis to metabolize glucose for energy and NADPH oxidase to generate ROS. Accordingly, we show that uremia impaired ROS production and fungicidal activity of neutrophils. The neutrophils in the presence of uremic serum show aberrant activation of Glycogen synthase kinase 3? (GSK3β), a negative regulator of mTOR dependent Glut1 expression and glucose uptake in the cells. Interestingly, pharmacological inhibition of GSK3β restored Glut1 expression and glucose uptake and antifungal activity of neutrophils in uremia. We identified para-cresol, a major toxin in the serum of uremic humans and mice, aberrantly inhibits GSK3β/mTOR pathway in neutrophils. Finally, we were able to demonstrate that serum from hemodialysis patients with renal disease suppressed the antifungal function of healthy donor neutrophils, an effect less apparent post-dialysis.

**Conclusion:** Our data reveal that uremia suppresses the candidacidal function of neutrophils by affecting glucose metabolism and subsequently ROS generation. Our discovery of a link between the aberrant function of GSK3β and neutrophil dysfunction in uremia suggests a previously unanticipated approach for the treatment of this fatal infection in patients with kidney disease.
**Introduction:** Arterial calcification due to deficiency in CD73 (ACDC) is a recessive disease due to biallelic mutations in NT5E, which encodes CD73. ATP is released from cells under stress (e.g., mechanical stress) and rapidly broken down by extracellular enzymes. CD73 is the final step of this process, converting AMP to adenosine, which allows cells to adapt to the ATP-releasing stress. ACDC patients exhibit tortuous peripheral arteries, dysregulation of the internal elastic lamina, and extensive medial vascular calcification that seems to nucleate at elastic fiber break points. These structural changes in extracellular matrix are a hallmark of aneurysmal disease, and TGF-ß signaling is thought to promote aneurysm formation. We hypothesize that deficiency in CD73-mediated adenosine receptor signaling potentiates TGF-ß signaling, resulting in matrix dysregulation.

**Methods:** Primary human aortic smooth muscle cells (SMCs) and SMCs from CD73KO and WT mice were isolated and used in these studies. Human cells were treated with a CD73-specific inhibitor (PSB-14685 10uM). Cells were treated with exogenous human TGF-ß1 (1-5ng/mL), murine TGF-ß2 (5ng/mL), and adenosine receptor 2b agonist (A2bAR, 10uM). Elastin and lysyl oxidase (LOX) mRNA expression was measured using qPCR. Western blots were used to probe for SMAD2, SMAD3, SMAD1/5/8/9, p44/42, and p38. Levels of elastin protein expression were measured using immunocytochemistry (ICC) staining.

**Results:** Murine CD73KO SMCs expressed significantly more mTGF-ß2 mRNA at baseline compared to mWT SMCs. Elastin expression was higher in response to exogenous mTGF-ß2 in mCD73KO SMCs compared to mWT while LOX remained unchanged. Phosphorylation of SMAD2 was 2-fold higher in mCD73KO SMCs following mTGF-ß2 treatment in a single replicate. When testing for elastin protein expression, mCD73KO cells contracted and lifted after three days of treatment. Murine WT SMCs treated with mTGF-ß2 and A2bAR had complete reversal of elastin mRNA expression potentially by phosphorylation of p38 as it trended towards significance but not SMAD2, SMAD3, or p44/42. Pharmacologically blocking CD73 activity in human SMCs significantly enhanced hTGF-ß1 mediated elastin mRNA expression but not LOX. Both control and CD73-inhibitor groups had increased p-SMAD2 following hTGF-ß1 treatment, but there were no differences. Human SMCs treated with the CD73 inhibitor and hTGF-ß1 trended towards higher elastin expression by ICC in two replicates, but further replicates are warranted.

**Conclusion:** These data suggest that CD73-mediated adenosine signaling can modulate TGF-ß matrix expression potentially via noncanonical pathways, which has not been described in previous literature. TGF-ß matrix expression seems to be reversible via AR2B agonism via noncanonical pathways.
**Poster Abstracts**

**26-B Poster:** Examining Potential Biomarkers in Early Diffuse Scleroderma Patients Treated with Statins

**Presenter:** Erika Joyce, Clinical Fellow

**Research Interest:** Bench (Basic Science)
Rheumatology and Clinical Immunology

**Mentors:** Robyn Domsic MD

**Funding Source:** none

**Authors:** Erika Joyce DO, Robyn Domsic MD

**Introduction:** Systemic Sclerosis (SSc) is a multisystem autoimmune disease with the highest case specific mortality among connective tissue diseases. Pathogenesis remains elusive but involves complex interplay of vascular injury, immune system activation and excessive fibrosis all resulting in endothelial cell dysfunction. Statin medications remain one of the most frequently utilized therapies for vascular injury secondary to atherosclerotic disease. Additional benefits of statins include improved endothelial cell function, reduced inflammatory response and fibrosis, plaque stability and antithrombotic effects. Limited data also suggests statins may improve vascular function in SSc patients. Our study aims to whether treatment with statin therapy is associated with changes in potential vascular biomarkers in SSc patients.

**Methods:** Samples were collected as part of a single-center randomized control trial evaluating the effect of atorvastatin therapy on vascular endothelial function and Raynaud phenomenon symptoms in early stage diffuse SSc patients. Baseline and 16 week samples will be analyzed for expression for a comprehensive panel of potential biomarkers of endothelial cell dysfunction via ELISA and for circulating endothelial progenitor cells via flow cytometry. These expression patterns will be compared to those found in serum samples 16 weeks following statin vs placebo therapy. T-tests or appropriate non-parametric comparisons will be made where appropriate. Correlative analysis will also be performed between biomarkers and vascular imaging.

**Results:** 24 patients were enrolled in the trial. The population was 80% female and 88% Caucasian, in keeping with the Pittsburgh SSc population. The average age at first visit was 52.7 years. No patient had prior diabetes or cardiovascular disease. Serum samples from baseline and 16 weeks post statin therapy have been collected and are currently being analyzed.

**Conclusion:** This data may provide insight into the biological impact of statin therapy upon endothelial cell dysfunction in different vascular beds of SSc patients. This could clarify the role of a new class of therapy for SSc patients, and provide the basis for further investigative mechanistic studies if future investigational trials in statin therapy are performed.
**27-B Poster:** In Erythroblasts, Heme Regulates the Expression of Placenta Growth Factor, a Contributor to Pulmonary Hypertension in Sickle Cell Disease, Through the Oxidant Response Transcription Factor NRF2

**Presenter:** Maria Kapetanaki, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Gregory Kato MD

**Funding Source:** HLBVMI, Div. of Hem-Onc., and ITxM

**Authors:** Maria Kapetanaki PhD, Oluwabukola Gbotosho PhD, Deva Sharma MD, Valerie Schrott MS, Frances Weidart MS, 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 (PIGF) 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. Our lab’s published work has demonstrated the heme-bound iron (hemin) stimulation of the PIGF promoter in human K562 cells and in primary human erythroid cells. This project focuses on identifying the key factors that are activated by heme and are involved in the PIGF upregulation in erythroid cells.

**Methods:** Cell Culture: Human erythroid cells (K-562 cells) were treated with i) hemin for up to 24 hours ii) Brusatol iii) siRNA against Nrf2 and MafG. Brusatol can inhibit Nrf2-mediated defense mechanism. Mouse hematopoietic stem cells expanded in serum-free media for 4 days, followed by EPO-induced differentiation and hemin treatment for 7 days. Mouse experiments: Mice were infused with hemin for 3 hours. Real time qPCR: Transcripts were quantified using Taqman Gene Expression Assays from ABI. Relative expression changes were calculated with the DeltaDeltaCt method. Statistical significance was calculated using a two-way ANOVA test. P values: *<0.01, **<0.01, ***<0.001.

**Results:** Our current data reveal that heme induces PIGF through the Nrf2 antioxidant response mechanism and regulates the expression of several members of this pathway. Gene expression knockdown and small molecule inhibitor and activator experiments have revealed a central role of Nrf2 in activating the PIGF promoter in response to heme, which was further supported by chromatin immunoprecipitation experiments. While PIGF regulation shows a few common aspects to HO-1 regulation, we have observed significant differences as well, mainly involving the role of BACH-1. In addition to the extensive experimental data from our human cell models, we have established a murine primary cell model of heme treatment as well as an in vivo murine model of heme overdose where we are able to assess both the stimulation of PIGF expression and the contribution of the antioxidant response pathway during that stimulation.

**Conclusion:** Our results to date support a mechanism in which accelerated heme turnover in SCD promotes robust expression of PIGF 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.
**28-B  Poster:** Selective Deletion of MyD88 in B cells after Disease Onset is Therapeutically Efficacious in a model of Systemic Lupus Erythematosus

**Presenter:** Minjung Kim (Katie), Research III

**Research Interest:** Bench (Basic Science)
Rheumatology and Clinical Immunology

**Mentors:** Jeremy Tilstra MD

**Funding Source:** K12/R01

**Authors:** Minjung (Katie) Kim MS, Claire Leibler, MD, Tony Marinov PhD, Kevin Nickerson PhD, Jeremy Tilstra MD

**Introduction:** Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease that affects various organs in the body. Inflammations caused by SLE damages are prominent in kidney, skin, joints, central nervous system, lungs, and hematopoietic system. Such damages causes fatigue, muscle pain, fever, and skin rashes in patients, and thus impair quality of life. Myeloid differentiation primary response 88 (MyD88) is a central immune adaptor protein. MyD88 regulates both TLR7 and TLR9 signaling, which in turn are mediators of disease in systemic lupus erythematosus (SLE). Lupus prone murine mice (MRL.Faslpr) develop autoantibodies, proteinuria, dermatitis, and glomerulonephritis. However, MyD88 deficient mice (MyD88−/−) exhibit ameliorated disease symptoms including minimal organ damage and reduced autoantibody formation. These features were recapitulated in B cell specific MyD88 deficient mice. What remains unknown is whether MyD88 in B cells plays a role in disease initiation and/or perpetuation.

**Methods:** The onset of the disease in the MRL.Faslpr lupus model is between 9 to 11 weeks of age. We used hCD20-Tam Cre mice crossed with MyD88floxed mice, in which depletion of B cell specific MyD88 is induced by tamoxifen, to study the effect of MyD88 deficiency after disease onset. Tamoxifen was orally administered biweekly (1mg/mouse) through oral gavage starting when the mice were 12 weeks of age. Deletion of MyD88 within the B cell compartment was confirmed via qPCR.

**Results:** Specificity was assessed by evaluating the T cell and myeloid compartment, which showed no deletion. Additionally, B cells from treated mice showed abrogated signaling when stimulated with TLR9 ligands as expected. Most notably, mice with a B cell specific deletion of MyD88 (B-MyD88−/−) exhibited a significant survival advantage over control mice. B-MyD88−/− mice had reduced autoantibody formation as assessed for anti-RNA and anti-DNA. The B-MyD88−/− mice also had reduced renal disease as assessed by histology that included both glomerulonephritis and interstitial inflammation.

**Conclusion:** These experiments suggest that there is a continued role for B cell signaling throughout the course of disease in MRL.Faslpr lupus prone mice. Furthermore, this portends that targeting MyD88 or its upstream targets such as TLR7/9 in B cells may be a viable therapeutic option in SLE. We will next administer tamoxifen to the mice, starting from 15 weeks of age, to assess the therapeutic range of this intervention.
**Poster Abstracts**

**29-B Poster:** High Content Screening of Novel Regulators of Pro-Fibrotic Signaling in Scleroderma

**Presenter:** Travis Lear, Graduate Student

**Research Interest:** Bench (Basic Science)
Aging Institute

**Mentors:** Bill Chen PhD

**Funding Source:** F31

**Authors:** Travis Lear BA, Karina Lockwood, Christina Morse BS, Daniel Kass MD, Rama Mallampalli MD, Robert Lafyatis MD, Bill Chen PhD

**Introduction:** Systemic scleroderma (SSc) is an autoimmune disease of unknown cause and affects over 2.5 million people globally. SSc results in dysfunctional connective tissues, which affects many organs including skin, cardiovascular, and particularly the lung. This results in excessive fibrous production; the resultant pulmonary fibrosis is the main cause of mortality. There are no approved medicines to treat lung SSc. Recent research suggests that expression of the cytokine TGF-b drives disease status. TGF-b stimulates pro-fibrotic signaling through SMAD-mediated gene expression. Further, SSc manifests as accelerated aging, with increased cellular senescence, impaired autophagy, and dysfunctional mitochondria (1). Indeed, a recent review implicates mitochondrial dysfunction as a driver of SSc pathology (2).


**Methods:** We utilized primary lung fibroblast cultures from SSc patients to conduct high content automated microscopy screening. Cultures were transfected with an siRNA library against ubiquitin E3 ligases and a subset of kinases. Following knockdown, cells were treated with TGFb prior to immunocytochemistry and detection of SMAD2/3 localization. A ratio of nuclear to cytosolic SMAD signal was calculated, and siRNA targets were ranked by their translocation scores.

**Results:** We screened a siRNA library targeting Ubiquitin E3 ligases and protein kinases for their effects on impairing SMAD2/3 translocation and observed several candidate hits: E3 ligases KLHL42 and RNF216, and PIK3C3 kinase. Interestingly, PIK3C3 is linked to initiation of autophagy and regulation of mitophagy. Their silencing reduced SMAD activation and the production of fibrous materials such as smooth muscle actin and fibronectin.

**Conclusion:** Here we report new regulators of SSc pro-fibrotic signaling, whose characterization may open new avenues of research and development of SSc therapy. Further studies will characterize the role and nature of this link between SSc, aging, and mitochondrial health.
**30-B Poster: Tead1 is required for perinatal cardiomyocyte proliferation**

**Presenter:** Ruya Liu, Junior Faculty

**Research Interest:** Bench (Basic Science)
Endocrinology and Metabolism

**Mentors:** Mousumi Moulik MD

**Funding Source:** K08/R01

**Authors:** Ruya Liu MD, Rajaganapti Jagannathan PhD, Feng Li, Jeongkyung Lee PhD, Nikhil Balasubramanyam BSc, Byung Kim BSc, Ping Yang MD, Vijay Yechoor MD, Mousumi Moulik MD

**Introduction:** Adult heart size is determined predominantly by the cardiomyocyte number and size. The cardiomyocyte number is determined primarily in the embryonic and perinatal period, as adult cardiomyocyte proliferation is restricted in comparison to that seen during the perinatal period. Recent evidence has implicated the mammalian Hippo kinase pathway as being critical in cardiomyocyte proliferation. Though the transcription factor, Tead1, is the canonical downstream transcriptional factor of the hippo kinase pathway in cardiomyocytes, the specific role of Tead1 in cardiomyocyte proliferation in the perinatal period has not been determined.

**Methods:** We generated Tead1 flox mice, wherein, Tead1 exon 3, which encodes the DNA binding domain, is floxed. Crossing these mice with transgenic mice that carry the Cre-recombinase driven by the cardiomyocyte specific Myh6 promoter resulted in cardiomyocyte specific deletion of Tead1 (Tead1-cKO mice) starting in the embryonic period after embryonic day 15.5. We also generated Tead1 deletion in a mouse cardiomyocyte cell line using CRISP-Cas9 system to study the function of Tead1 in proliferation in a cell autonomous manner. Proliferation was assessed by assessing expression of Ki67 and phosphor-Histone 3 (pH3), in vivo, and by cell doubling studies, in vitro. qPCR and western blotting was used to delineate underlying mechanisms.

**Results:** Perinatal cardiomyocyte-specific Tead1 deletion was lethal by postnatal day 9 in Tead1-cKO mice due to dilated cardiomyopathy. These Tead1-cKO mice had significantly decreased fractional shortening and ejection fraction on echocardiograms of the heart at day 1 post-natally. On section there was significant chamber enlargement with wall thinning in the Tead1-cKO hearts. While there was no significant change in apoptosis, Tead1-deficient cardiomyocytes have significantly decreased proliferation, as assessed by Ki67 incorporation (all phases including G1-S-G2-M but not G0) and by pH3 staining (M phase) during the immediate postnatal period, when proliferation rate is normally high. Deletion of Tead1 in HL-1 cardiac cell line led to a significant decrease in cell doubling time, confirming that cell-autonomous Tead1 function is required for normal cardiomyocyte proliferation. This was secondary to significant decrease in levels of many proteins, in vivo, that normally promote cell cycle in cardiomyocytes at cell cycle stages including G1-S and G2/M.

**Conclusion:** Taken together this demonstrates the non-redundant critical requirement for Tead1 in regulating cell cycle proteins and proliferation in cardiomyocytes in the perinatal heart.
**Introduction:** Non-alcoholic fatty liver disease (NAFLD), a lifestyle disease of the western world, is classified into a simple steatosis or non-alcoholic fatty liver (NAFL) and a progressive non-alcoholic steatohepatitis (NASH). The outcome of NAFLD is determined by the degree of fibrosis rather than steatosis or inflammation. Therefore, identifying the mechanisms that drive hepatic fibrosis is crucial to combat the progression of NAFLD. The epidemic in obesity is the key causal factor for the increase in NAFLD. Obesity is often associated with chronic activation of hypoxia signaling in various tissues including liver.

**Methods:** Liver specific HIF2 alpha knockout mice was created using cre-lox P system. Littermates were randomly distributed into two groups and fed with methionine sufficient and methionine deficient diet was fed respectively. Hepg2 cells were maintained under methionine depleted medium for 12h. Western blotting and immunofluorescence was performed foe HIF2a.

**Results:** Hypoxia signaling is mediated by the transcription factor, hypoxia inducible factor (HIF) -1a and HIF-2a. We have demonstrated that chronic activation of hepatic HIF-2a, but not HIF-1a, is sufficient to induce dyslipidemia, hypercholesterolemia and spontaneous steatohepatitis. Moreover, hepatic fibrosis is attenuated in mice with liver-specific disruption of HIF 2a suggesting a key role for hepatic HIF-2a in fibrosis. However, the molecular mechanisms that induce hepatic HIF-2a are not known. When we fed the mice with methionine deficient (MCD) diet, the induction of fibrosis is associated with the periportal expression of HIF-2a in liver. Moreover, depletion of methionine induced HIF-2a expression in liver cell lines suggesting a cell-autonomous role for methionine in HIF-2a expression. Further investigation is underway to determine the mechanism by which HIF-2a induce fibrosis in NASH models.

**Conclusion:** Targeting hepatic HIF2a could be a therapeutic strategy to control NASH progression.
**Poster: Phenotyping a Mouse with Vascular Smooth Muscle Specific Deletion of the Gamma Epithelial Sodium Channel (?ENaC)**

**Presenter:** Mahpara Hasan Mutchler, Undergraduate Student

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Thomas Kleyman MD

**Authors:** Mahpara Hasan, Stephanie Mutchler BS, Roderick Tan MD, Thomas Kleyman MD

**Introduction:** Previous work has shown that ENaC plays an important role in mediating myogenic tone of blood vessels. Additionally, mice with whole body knockdown of βENaC surprisingly show an increased blood pressure, potentially due to the loss of myogenic tone in the renal vasculature leading to inflammation and glomerular damage. However, because these results were obtained in an animal with global protein down regulation, the contributions of vascular smooth muscle (VSM) ENaC cannot be separated. To address this, we have created a VSM ENaC knockout animal using cre-lox technology and have begun conducting renal and vascular phenotyping experiments.

**Methods:** Mice were generated using cre-lox technology. Blood pressure was assessed using radiotelemetry, isolated vessels were studied with pressure myography, and glomerular filtration rate was analyzed with a transcutaneous probe. Ischemia reperfusion injury was done by clamping the renal artery and excising the contralateral kidney.

**Results:** Contrary to the βENaC hypomorphs, these mice did not have increased baseline blood pressure, as measured by radiotelemetry. We also did not observe significant differences in myogenic response of the mesenteric or thoracodorsal arteries, although the data is only preliminary. We did observe preliminarily that the knockout animals appear to have increased glomerular filtration rate (GFR) in female animals, and that the knockouts have more protein in the urine with a 4-week treatment of aldosterone and high salt diet. However, these animals do not display a universal increased susceptibility to injury as they behaved relatively the same as controls under conditions of renal ischemia reperfusion injury as assessed by serum creatinine levels and mRNA levels for kidney injury markers NGAL and Kim1.

**Conclusion:** Taken together, these data reveal that VSM ?ENaC may be playing a distinct role from that of βENaC, potentially only contributing to the myogenic response in the microvasculature of the kidney under conditions of stress. However, further analysis is needed to increase the significance of this preliminary work.
**Poster**: Epithelial Sodium Channel (ENaC) in Endothelium Modulates Vascular Reactivity with a High Salt Diet

**Presenter**: Stephanie Mutchler, Graduate Student

**Research Interest**: Bench (Basic Science)
Renal-Electrolyte

**Mentors**: Thomas Kleyman MD

**Funding Source**: T32

**Authors**: Stephanie Mutchler BS, Thomas Kleyman MD

**Introduction**: Recent work has shown that ENaC in the endothelium is involved in vascular dysfunction in the setting of high fat diet and increased aldosterone. However, the effects of endothelial ENaC in the setting of high salt diet (HSD) remain relatively unknown, especially in mouse models. Therefore, we aimed to investigate the effects of chronic HSD (8 weeks) on vascular health.

**Methods**: Pressure myography was used to assess vascular function. Blood electrolyte content was analyzed using an iSTAT system, and plasma aldosterone was measured with an ELISA.

**Results**: We found that 8 weeks of HSD significantly reduced acetylcholine (Ach) responsiveness in the thoracodorsal artery (TDA) of mice. This dysfunction was ameliorated when 5µM amiloride, an ENaC inhibitor, was added to the lumen of the vessels. In vessels taken from animals fed a control diet (0.4% NaCl), the addition of amiloride had no effect on Ach-mediated vasodilation. Additionally, amiloride did not significantly alter sodium nitroprusside or phenylephrine response in the 8 week HSD vessels, suggesting amiloride is directly affecting endothelial function, potentially through altered nitric oxide release. The mice fed an 8 week regimen of HSD had significantly higher serum sodium with decreased plasma aldosterone levels, suggesting that increased aldosterone is not solely responsible for endothelial ENaC expression and function. Additionally, an endothelial-specific deletion of ?ENaC using an inducible cre-lox system, appears to offer protection from HSD-induced vascular dysfunction, as three of six control animals showed decreased responsiveness to Ach with 8 weeks of HSD whereas zero of the five knockout animals tested showed any dysfunction.

**Conclusion**: Taken together, these data demonstrate that endothelial ENaC plays a role in promoting the vascular dysfunction seen with chronic high salt intake. Ongoing studies will aim to elucidate the role of nitric oxide and eNOS phosphorylation status in this signaling pathway.
**Introduction:** With No Lysine (WNK) kinases are serine/threonine (S/T) kinases that regulate intracellular chloride concentration, cell volume, and blood pressure in mammals. The uniquely folded WNK kinase domain harbors an inhibitory halide binding pocket. A fall in intracellular chloride decreases Cl⁻ occupancy at this site, resulting in autoactivation and downstream phosphorylation of transporters that restore chloride concentrations back to normal. Given the observation that WNK kinases are present in both plants and animals, we hypothesized that this chloride sensing function emerged early in evolution.

**Methods:** To analyze WNK1 gene evolution, we gathered and aligned nucleotide and protein sequences from the UCSC Genome Browser and NCBI databases. 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. To measure chloride dependent inhibition, we cloned WNK kinase domain cDNAs into a bacterial expression vector; synthesized and purified them as GST fusion proteins in BL21 E. coli, and performed nonradioactive in vitro WNK kinase assays using the ADP-Glo system (Promega). Data were analyzed in GraphPad Prism.

**Results:** Phylogenetic reconstruction analysis revealed WNK-like kinase domains with putative halide binding sites in several protist species, including the choanoflagellate Salpingoeca rosetta, an evolutionary predecessor of premetazoan multicellularity. These findings were supported by homology modeling. In comparisons with the human WNK1 kinase domain, S. rosetta WNK1 exhibited weaker kinase activity, both at reaction concentrations of 15nM (mean difference = 198670 RLU, p = 0.03) and 75nM (mean difference = 3621044 RLU, p = 0.0005). When normalized to respective baseline activities, S. rosetta WNK1 exhibited greater chloride sensitivity, with a mean difference of 3.2 RLU (p <0.0001). The half maximal chloride inhibitory concentrations (IC50) for human and S. rosetta WNK1 were 18.63mM NaCl and 1.81mM NaCl, respectively.

**Conclusion:** These data indicate that S. rosetta possesses a bona fide WNK kinase. Though the activity of srWNK1 was low, it was exquisitely chloride-sensitive. This function was refined in metazoans through kinase domain evolution and gene duplication. Thus, our findings indicate that the chloride sensing function of WNK kinases is ancient, conserved, and essential for cellular viability.
35-B  **Poster:** Dual binding affinities for megalin and cubilin receptors accommodate wide variations in filtered albumin load

**Presenter:** Qidong Ren, Medical Student

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Ora Weisz PhD

**Funding Source:** Tsinghua MD Scholars Program

**Authors:** Qidong Ren Undergraduate, Youssef Rbaibi BS, Ossama Kashlan PhD, Ora Weisz PhD

**Introduction:** Albuminuria is one of the most important early symptoms and pathologic factors of kidney disease. The very small fraction of serum albumin that normally escapes the glomerular filtration barrier under physiologic conditions is efficiently recovered by the kidney proximal tubule (PT). Two multiligand receptors, megalin and cubilin, are expressed at the apical surface of PT cells and are believed to function together to internalize filtered albumin and other proteins via clathrin-mediated endocytosis. PT cells express a single high-affinity surface binding site for albumin with a Km similar to the estimated tubular concentration of 23 µg/mL (~0.4 µM). Although this site should be readily saturable, PT cells in vivo can readily internalize at least 50-fold higher concentrations of albumin.

**Methods:** We performed experiments to examine how the PT accommodates the uptake of albumin within this extraordinary range of physiologic to pathologic concentrations. Alexa Fluor 647 conjugate albumin uptake by spectrofluorometry assay in siRNA knock down cells and control cells. Droplet digital PCR for megalin and cubilin mRNA level expression analysis. Current studies to further test our hypothesis are focused on creating the high- and low-affinity albumin uptake sites by megalin or cubilin transfection of non-expressing cells, and assessing whether megalin: cubilin protein ratios in cells and kidney are consistent with the binding capacities of the low and high affinity uptake sites by Co-IP and western blot.

**Results:** Consistent with previous findings, only a single site was detected by surface binding of albumin on ice, whereas exposure of PT cells to increasing amounts of fluorescently-conjugated albumin at 37°C revealed a biphasic uptake profile. Deconvolution of the profile revealed two uptake sites for albumin with affinities of ~1.2 and 25 µM. Consistent with this, knockdown of cubilin using siRNA selectively reduced the binding capacity of the high-affinity site. Digital PCR to quantify the ratio of megalin:cubilin transcripts in mouse kidney revealed that megalin mRNA is expressed at higher levels than cubilin.

**Conclusion:** We hypothesized that cubilin and megalin receptors function independently of one another to mediate high- and low-affinity uptake of albumin under normal and pathologic conditions, respectively.
**Poster Abstracts**

36-B **Presenter:** Elizabeth Rochon, Post-Doctoral Scholar  
**Research Interest:** Bench (Basic Science)  
**Mentors:** Paola Corti PhD  
**Funding Source:** T32  

**Authors:** Elizabeth Rochon PhD, Maria Azzurra Missinato PhD, Jianmin Xue PhD, Jesus Tejero PhD, Michael Tsang PhD, Mark Gladwin MD, Paola Corti PhD

**Introduction:** Nitrite (NO2-) has been shown to have a beneficial effect on ischemia/reperfusion injury via the production of nitric oxide (NO) and modulation of reactive oxygen/nitrogen species (ROS/RNS). NO2- can be converted to NO by globin proteins via a nitrite reductase reaction. The role of NO2- and globins has not yet been investigated in the context of heart regeneration. Zebrafish can fully regenerate their hearts following injury and were used as a model to study the effects of hypoxia and NO2- treatment on regeneration. We hypothesize that treatment with hypoxia/NO2- will improve regeneration through increased production of NO or ROS/RNS.

**Methods:** We used an amputation and cryoinjury model to injure adult zebrafish hearts and tracked cardiac healing through immunofluorescence and histology. To determine the more global effect of hypoxia/NO2- treatment, we analyzed embryonic fin regeneration.

**Results:** We have found that NO2- treatment in hypoxia improves cardiomyocyte proliferation and neovascularization 5 days post amputation (dpa). We observe an increase in thrombocytes (1 dpa) and neutrophils (3 dpa) to the injured area and a decrease in the blood clot. Hypoxia and NO2- treatment resulted in improved blastema formation following embryonic fin amputation and increased thrombocyte and neutrophil recruitment. How NO2- is converted into either NO or another bioactive molecule is not understood in these contexts. We identified zebrafish Cytoglobin 1 (Cygb1) is a potential candidate; it is expressed in the epicardium and its expression is increased following cardiac injury.

**Conclusion:** These results suggest that NO2- treatment modulates the immune response to improve healing following cardiac injury and fin fold amputation, implicating a global improvement in healing capacity upon treatment with NO2- in hypoxia. Cygb1 may be mediating a regenerative response via its fast nitrite reductase rate (28.6 ± 3.1 M(-1) s(-1)) in its deoxy state or oxy-Cygb may react with NO2- to produce RNS, modulating the immune response this way. In the future we will identify the mechanism by which NO2- treatment modulates the immune response in the healing heart and determine if Cygb1 expression is necessary and/or sufficient for cardiac regeneration.
Poster: Aberrant Notch2 Signaling in the Vascular Endothelial Cell Leads to Increased Proliferation and Migration in Pulmonary Arterial Hypertension

Presenter: Sanghamitra Sahoo, Junior Faculty

Research Interest: Bench (Basic Science) VMI

Mentors: Patrick Pagano PhD

Funding Source: R01 (PJP)

Authors: Sanghamitra Sahoo PhD, Daniel de Jesus PhD, John Sembrat MSc, Mauricio Rojas MD, Elena Goncharova PhD, Patrick Pagano PhD

Introduction: Pulmonary arterial hypertension (PAH) develops when pulmonary vascular resistance rises sharply, leading to right heart failure and death. Most studies have focused on attenuating lung vessel constriction; however, little is known about the mechanisms controlling intimal proliferation and luminal obstruction. Numerous studies suggest that the Notch signaling influences vascular cell proliferation and migration, hallmark features of deleterious remodeling. Despite this, a role for Notch2 in PAH is entirely unknown. In this study, we hypothesize that hypoxia-induced repression of lung endothelial Notch2 results in increased EC proliferation/migration in PAH.

Methods: Human pulmonary artery endothelial cells (HPAEC) were grown in EBM-2 media components and incubated in either normoxia (21% oxygen) or hypoxia (1% oxygen) for requisite time. To gene silence Notch2, HPAECs were transfected with Notch2 siRNA or their scrambled control siRNA using the Lipofectamine 2000 transfection reagent. Gene silencing was confirmed after 72 hrs using immunoblotting and knock-down expressed as % of siRNA scrambled controls. All human lung and pulmonary artery tissue samples were de-identified with collection and processing approved by the Institutional Review Board of the University of Pittsburgh.

Results: In a hypoxia model replicating the PAH phenotype in vitro, HPAECs were subjected to 24 hrs hypoxia (1% O2) compared to normoxia (21% O2). Hypoxia attenuated Notch2 mRNA (0.64±0.02-fold vs. normoxia, p=0.0001) but did not affect other endothelial Notch receptors - Notch1 and 4. Furthermore, hypoxia decreased Notch2 protein levels (0.65±0.05-fold vs. normoxia, p<0.0001). q-RTPCR of lysates of pulmonary arteries from PAH patients showed marked reductions in Notch2 mRNA (0.30±0.08-fold vs. control patients, p<0.05). Immunofluorescence staining of lung sections of PAH patients showed reduced expression of Notch2 in the intima of the vessel wall compared to non-PAH samples. Notch2 siRNA under normoxic conditions increased EC migration in a “wound healing-scratch” assay (1.5±0.01-fold vs. scrambled control, p<0.05) and EC proliferation (1.2±0.07-fold vs. scrambled control, p=0.05) measured by CyQuant assay. Western blot analysis of signaling intermediaries showed decreased cell cycle inhibitor p21cip (0.54±0.05 vs. scrambled control, p<0.05), and increased levels of phospho-ERK1/2 (1.3±0.04-fold vs. scrambled control, p<0.001).

Conclusion: In the present study, we found that hypoxia suppressed Notch2 expression in the endothelium which appears to derepress ERK1/2 and downregulate p21cip leading to EC proliferation and migration. These data are consistent with a key modulatory role for Notch2 dysfunction in EC proliferation/migration and vascular remodeling in PAH. Data from human patients substantiates this dysfunction. The current study identifies a new signaling axis mediated by endothelial Notch2 that could contribute to pathophysiological changes associated with human PAH.
**Poster:** The nucleolus links acetyl-CoA fluctuations to p53-mediated stress responses

**Presenter:** Yusuke Sekine, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Aging Institute

**Mentors:** Toren Finkel MD

**Funding Source:** Aging Institute Seed

**Authors:** Yusuke Sekine PhD, Toren Finkel MD

**Introduction:** Acetyl-coenzyme A (acetyl-CoA) serves as a source metabolite for essential biomaterials such as ATP, fatty acids and sterols, but can also be directly utilized for protein acetylation. This latter function enables cells to modulate the activity of certain proteins and to reorganize chromatin in accordance with the cellular metabolic state. Altered acetyl-CoA metabolism is known to be involved in a wide range of pathophysiological conditions and recent evidence indicates its involvement in the aging and longevity of organisms. However, molecular mechanisms that directly respond to fluctuations in acetyl-CoA abundance, leading to activation of stress responses required to maintain cellular and metabolic homeostasis, are not fully understood.

**Methods:** We developed a novel culture cell system in which nucleo-cytoplasmic acetyl-CoA production is solely depending on acetate supplemented in the culture media, which enables us to control acetyl-CoA levels by simply manipulating the amount of acetate in the culture media. This was achieved through several experimental steps including the CRISPR-based gene editing of ATP citrate lyase (ACLY), the major enzyme involved in cytosolic acetyl-CoA generation. By using this cellular system, we have conducted multiple quantitative analyses including RNA seq, TMT-proteomics and acetylome analyses to understand global cellular responses following acetyl-CoA depletion.

**Results:** We found that acetyl-CoA depletion rapidly alters the integrity of nucleolus and thereby induces a nucleolar stress-dependent activation of p53. Moreover, this acetyl-CoA depletion-dependent nucleolar stress is mediated through Class IIa HDAC deacetylases, suggesting that HDAC-dependent deacetylation of nucleolar proteins plays a crucial role for maintaining nucleolar integrity.

**Conclusion:** These findings indicate an important role of the nucleolus as an organelle sensor converting acetyl-CoA fluctuations to p53-mediated stress responses.
**Introduction:** The polarized epithelial cells that comprise the proximal tubule (PT) have a specialized apical endocytic pathway that allows for high-capacity endocytosis which is necessary to recover essential nutrients and to maintain a protein-free urine. Megalin, a multi-ligand receptor at the apical surface of the epithelial cells, binds proteins in the ultrafiltrate and internalizes them via receptor-mediated endocytosis. Ligands are sorted from receptors in endocytic compartments, and the receptors are recycled back to the surface. The molecular identities of the compartments involved in sorting and recycling in PT cells and the kinetics of megalin trafficking through them are unknown. When endocytosis in the proximal tubule is dysfunctional, tubular proteinuria results. Dent disease, an X-linked disorder characterized by tubular proteinuria that progresses to renal failure, is caused by mutations in the Cl-/H+ exchanger CLC-5. Loss of CLC-5 has been shown to reduce endocytic uptake and to decrease megalin protein expression without altering mRNA levels. However, the mechanism by which this occurs is unclear.

**Methods:** We previously discovered that OK cells cultured under continuous fluid shear stress develop morphological and functional features similar to that of the PT in vivo, including high apical endocytic capacity and increased megalin expression. We used data obtained through biochemical approaches to estimate endocytic and recycling rates and the half-life of surface megalin in untreated and CLC-5 knockdown OK cells. These rates were used to construct a simplified model of megalin trafficking in differentiated PT cells.

**Results:** We present an ordinary differential equation (ODE) model of megalin trafficking describing surface and internalized pools of megalin with estimated kinetic parameters. We observed a greater fraction of internalized megalin compared to the surface pool due to an endocytic rate that is much faster than the recycling rate. We have quantified decreases in megalin expression and surface half-life with loss of CLC-5 expression.

**Conclusion:** Current and future work includes quantifying alterations in megalin trafficking in CRISPR/Cas9 mediated CLC-5 KO models and defining the structure and markers of the apical endocytic pathway by quantitative imaging to expand our model to include additional trafficking steps. This model will then be used to predict which steps in megalin trafficking are altered in Dent disease.
Development of a Human in Vitro Model of Lung Epithelial Senescence Highlights the Cell-Type Specific Response to Telomere Dysfunction

Presenter: Daniel Sullivan, Clinical Fellow

Research Interest: Bench (Basic Science) Pulmonary, Allergy and Critical Care Medicine

Mentors: Jonathan Alder PhD

Funding Source: T32

Authors: Daniel Sullivan MD, Mark Roth BS, Jonathan Alder PhD

Introduction: Cellular senescence is a central process in aging and has been hypothesized to play a role in age-associated diseases, including idiopathic pulmonary fibrosis. Many transcriptional, morphologic, and secretory changes have been described when cells undergo senescence. We sought to create a human type 2 alveolar epithelial cell-line where senescence could be induced conditionally. We selected a model of telomere dysfunction to force human A549 cells into cellular senescence. Our hypothesis was that utilizing a model of telomere dysfunction in a human p53-competent cell line would be an ideal context to explore the cellular consequences of senescence in a relevant cell-type.

Methods: A tetracycline-inducible A549 cell line that conditionally expresses dominant negative human TRF2, hereafter referred to as TRF2-DN, was generated. Cell growth, clonogenic potential, gene expression, and morphologic changes were characterized using standard methods. Genomic wide expression changes were measured using RNA-seq.

Results: Western blotting verified overexpression of the dominant negative protein in the induced TRF2-DN cell line. Proliferation studies indicated defective cell growth 7 days following induction. Induction of TRF2-DN expression severely compromised the clonogenic potential of A549 cells (p<0.001), but did not induce apoptosis. Induction of TRF2-DN expression led to morphologic changes consistent with senescence, and cells were positive for senescence-associated beta-galactosidase. Senescence induced expression of the previously reported senescence-associated secretory phenotype proteins, including IL8 (+4400%) and CLXL1 (+2900%). Major changes were also seen in cellular adhesion, apoptotic, and lipid maintenance pathways.

Conclusion: A dominant negative mutation in a component of the shelterin complex is an effective strategy to induce senescence in an immortalized model of a human alveolar epithelial cell. Preliminary results suggest that gene expression changes observed are distinct from the changes that have been described in fibroblasts. The known and novel gene expression changes seen in various cellular processes will serve as targets for further investigation into cellular senescence and highlight the cell-type and context-specific responses to telomere dysfunction and cellular senescence.
**41-B Poster: TBK1/IKKe inhibitor Amlexanox blocks Multiple Myeloma cell growth in vitro and in vivo**

**Presenter:** Quanhong Sun, Junior Faculty

**Research Interest:** Bench (Basic Science)  
Hematology/Oncology

**Mentors:** Deborah Galson PhD

**Funding Source:** RO1

**Authors:** Quanhong Sun PhD, Peng Zhang PhD, Juraj Adamik PhD, Konstantinos Lontos MD, Valentina Marchica PhD, Nicola Giuliani PhD, Rebecca Silbermann MD, David Roodman MD, Lea Nyiranshuti PhD, Joseph Latoche PhD, Carolyn Anderson PhD, Kostantinos Verdelis PhD, Deborah Galson PhD

**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 of bone. 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 FACS and a MM mouse model to examine this hypothesis.

**Results:** We found that TBK1 knockdown in BMM by shRNA significantly attenuated the ability of MM conditioned media (MM-CM) to increase OCL differentiation over control media. However, the TBK1/IKKe inhibitor Amlexanox (Amlx) blocked both normal and MM-enhanced OCL formation. Further, Amlx treatment of primary BMSC from MM patients or normal donors decreased expression of TNFa, IL-6 and RANKL, thereby decreasing BMSC support of MM survival and OCL differentiation. These data suggest that Amlx treatment in vivo would reduce bone microenvironmental MM support. We found that TBK1 mRNA and protein expression in CD138+ plasma cells from patients increased with MM progression. Therefore, we tested whether Amlx would also affect MM cells. We found that Amlx strongly decreased the viability of several MM cell lines and primary MM cells via induction of apoptosis. Amlx treatment of MM cell lines also induced a G1/S blockade, decreased activated ERK1/2, and increased translation of the dominant-negative C/EBP?LIP isoform in several MM cell lines. The positive-acting C/EBP?-LAP isoform was previously shown to be a critical transcription factor for MM viability. Amlx also enhanced the effectiveness of the proteasome inhibitors bortezomib and carfilzomib to kill MM cells in culture. Importantly, oral Amlx dose-dependently inhibited tumor growth in a syngeneic immunocompetent MM mouse model (STGM1 MM cells expressing GFP and secreted GLuc injected intratibially into C57Bl/KaLwRij). Tumor growth was assessed by longitudinal analyses of secreted GLuc levels in the blood and PET-CT. The high dose Amlx anti-tumor effect size was similar to Bortezomib treatment, which was confirmed by FACS analyses of %GFP+ MM cells in the tibiae. Fewer OCL were formed from BMM isolated from Amlx-treated mice. MicroCT analyses of the bone structure will be forthcoming.

**Conclusion:** These data suggest that Amlx targeting of TBK1/IKKe signaling may decrease MM bone disease by slowing MM growth, directly and indirectly, and protect the bone from MM-induced osteolysis.
Poster: Deficiency of BOLA3 regulates mitochondrial and glycine metabolism in pulmonary hypertension

Presenter: Yi Yin Tai, Research III

Research Interest: Bench (Basic Science) VMI

Mentors: Stephen Chan MD PhD

Funding Source: NIH and AHA

Authors: Qiujun Yu MD, Yi Yin Tai MS, Ying Tang MS, Jingsi Zhao MS, Vinny Negi PhD, Miranda K Culley BA, Jyotsna Pilli PhD, Wei Sun MD, Karin Brugger MD, Johannes Mayr MD, Rajeev Saggar MD, Rajan Saggar MD, W. Dean Wallace MD, David J Ross MD, Aaron B. Waxman MD

Introduction: Iron-sulfur (Fe-S) cluster deficiencies have been linked to pulmonary hypertension (PH). BolA Family Member 3 (BOLA3), an important regulator of Fe-S cluster biogenesis, regulates oxidative mitochondrial processes and synthesis of lipoic acid, a key post-translational moiety controlling glycine biosynthesis. Mutations in BOLA3 result in multiple mitochondrial dysfunction syndrome, a fatal disorder associated with PH. However, mechanisms by which BOLA3 drives this disease are not defined.

Methods: Human pulmonary arterial endothelial cells (PAECs) were studied primarily, along with various hypoxic rodent models with RNA-mediated knockdown or virus-mediated overexpression of BOLA3.

Results: In PAECs as well as lungs from human Group 1 and Group 3 PH patients and multiple rodent models of PH, BOLA3 expression was downregulated via a HIF-2a-HDAC-mediated epigenetic axis. In vitro studies in PAECs showed that BOLA3 deficiency decreased Fe-S integrity, impairing mitochondrial complexes and lipoate-contained 2-oxoacid dehydrogenases with consequential increase in glycolysis and alteration in mitochondrial respiration. Via either RNA knockdown or naturally occurring human genetic mutation, BOLA3-deficient cells also showed down-regulated expression of lipoate-dependent glycine cleavage system H protein (GCSH), with elevated accumulation of intracellular glycine. Downstream of altered oxidative metabolism and glycine levels, BOLA3 deficiency increased endothelial proliferation and vasoconstriction, while reducing apoptosis and angiogenesis. RNA-mediated knockdown of endothelial BOLA3 and virus-mediated overexpression of BOLA3 in mouse vasculature in vivo demonstrated that BOLA3 deficiency promotes PH with increased pulmonary vascular remodeling and worsened hemodynamics. Importantly, chronic in vivo supplementation of glycine reversed the protective effects of forced expression of BOLA3 in PH, thus proving that glycine upregulation is essential for the control of PH by BOLA3 deficiency.

Conclusion: BOLA3 deficiency plays a critical role in promoting endothelial dysfunction and PH via impairment of mitochondrial oxidative respiration and glycine metabolism. These results provide molecular insights for clinical associations of PH with hyperglycinemic syndromes and mitochondrial disorders and identify novel metabolic targets involved in epigenetics, Fe-S cluster biogenesis and glycine homeostasis for diagnostic and therapeutic development.
**Poster: IL-36 and IL-1 drive immunity to oral candidiasis via parallel mechanisms**

**Presenter:** Jamie Tweedle, Post-Doctoral Scholar

**Research Interest:** Bench (Basic Science)  
Rheumatology and Clinical Immunology

**Mentors:** Sarah Gaffen PhD

**Funding Source:** T32

**Authors:** Jamie Tweedle PhD, Akash Verma PhD, David Moyes PhD, Sarah Gaffen PhD

**Introduction:** Protection against microbial infection by the induction of inflammation is a key function of the IL-1 superfamily, including both classical IL-1 and the new IL-36 cytokine families. Candida albicans is a frequent human fungal pathogen causing mucosal infections. Although the initiators and effectors important in protective host responses to C. albicans are well described, the key players in driving these responses remain poorly defined. Recent work has identified a central role played by IL-1 in inducing innate Type-17 immune responses to clear C. albicans infections. Despite this, lack of IL-1 signaling does not result in complete loss of immunity, indicating that there are other factors involved in mediating protection to this fungus. In this study, we identify IL-36 cytokines as a new player in these responses.

**Methods:** To investigate the role of IL-36 in response to OPC, mice were challenged sublingually with C. albicans. Tongue homogenates were prepared 2 days post-infection (p.i.), and total mRNA was subjected to qRT-PCR. Signaling mechanism was assessed in vitro. TR146 human oral epithelial cells were challenged with C. albicans. Gene expression was assessed by qRT-PCR and protein was assessed by Western blot and ELISA.

**Results:** We show that C. albicans infection of the oral mucosa induces the production of IL-36. As with IL-1α/β, induction of epithelial IL-36 depends on the hypha-associated peptide toxin Candidalysin. Epithelial IL-36 gene expression requires p38-MAPK/c-Fos, NF-κB, and PI3K signaling and is regulated by the MAPK phosphatase MKP1. Oral candidiasis in IL-36R-/- mice shows increased fungal burdens and reduced IL-23 gene expression, indicating a key role played by IL-36 and IL-23 in innate protective responses to this fungus. Strikingly, we observed no impact on gene expression of IL-17 or IL-17-dependent genes, indicating that this protection occurs via an alternative pathway to IL-1-driven immunity.

**Conclusion:** Thus, IL-1 and IL-36 represent parallel epithelial cell-driven protective pathways in immunity to oral C. albicans infection.
**Poster Abstracts**

**44-B Poster:** The Macrophage Response to Klebsiella Pneumoniae Involves CD36-mediated Syk Activation And Type I IFN-dependent Cytokine Production

**Presenter:** Rick van der Geest, Graduate Student

**Research Interest:** Bench (Basic Science)
- Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Janet Lee MD

**Funding Source:** R01 to JSL (NIH HL086884, HL136143, HL142084)

**Authors:** Rick van der Geest MSc, Huihua Li MD, Janet Lee MD

**Introduction:** CD36 is a scavenger receptor that recognizes multiple ligands, including several PAMPs (e.g. diacylated lipopeptides) and DAMPs (e.g. amyloid β). CD36 provides host protection against pulmonary infection with Klebsiella pneumoniae (KP) by amplifying KP-induced cytokine production in macrophages. Mice that lack CD36 display significantly attenuated IFN-γ and IL-12 production in the lung during KP infection, suggesting that CD36 may be involved in the regulation of type II IFN responses. Yet, the molecular mechanism via which CD36 promotes cytokine production is not well understood. We hypothesized that CD36 regulates KP-induced cytokine responses through type II IFN signaling.

**Methods:** Microarray analysis was performed to identify global changes in gene expression in WT and Cd36-/- macrophages exposed to KP. ELISA was used to determine the impact of IFNAR, IFNGR and FcR? deficiency as well as Syk inhibition on KP-induced cytokine production. Western blot was used to evaluate MAPK, NF-kB and Syk activation in WT and Cd36-/- macrophages in response to KP.

**Results:** Transcriptomic profiling indicated that exposure of macrophages to KP induced a type I and type II IFN gene expression profile, which was impaired in Cd36-/- macrophages. Interestingly, while the KP-induced cytokine response was similar in WT and Ifngr1-/- BMDMs, Ifnar1-/- BMDMs displayed aberrant KP-induced gene expression and protein production of TNFa, IL-6, IL-12p40 and CXCL10 compared to WT BMDMs, and thus phenocopied Cd36-/- macrophages. While KP-induced activation of MAPK and NF-kB signaling was similar in WT and Cd36-/- macrophages, activation of Syk was markedly impaired in Cd36-/- macrophages. Moreover, pharmacological inhibition of Syk abolished KP-induced cytokine production in WT macrophages, suggesting that Syk is involved in the proximal control of the macrophage cytokine response to KP. As CD36 was previously shown to couple to the transmembrane adaptor FcR? to engage Syk, we examined KP-induced cytokine production in BMDMs that lack FcR?. Interestingly, the KP-induced cytokine response of Fcrlg-/- macrophages did not phenocopy that of Cd36-/- macrophages, suggesting that CD36 engages an alternative adaptor to mediate KP-induced cytokine responses.

**Conclusion:** Our data indicate that CD36 mediates KP-induced Syk activation, which we show is necessary for optimal KP-induced cytokine responses in macrophages. In addition, we show that autocrine type I IFN signaling is required for effective KP-induced cytokine production. We speculate that CD36-mediated amplification of the KP-induced cytokine response in macrophages involves a Syk-dependent signaling cascade that leads to the induction of a type I IFN response.
Poster: Effect of Myocardial Infarction on Insulin Resistance: Role of Visceral Adipose Tissue Macrophage Subsets

Presenter: Sathish Vasamsetti, Post-Doctoral Associate

Research Interest: Bench (Basic Science) VMI

Mentors: Partha Dutta PhD

Funding Source: PI's grant

Authors: Sathish Vasamsetti PhD, Emilie Coppin PhD, Xinyi Zhang MD, Jonathan Florentin PhD, Partha Dutta PhD

Introduction: Myocardial infarction (MI) is the leading cause of cardiac associated mortalities. 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). But the mechanistic underpinnings of IR after MI are poorly explored.

Methods: We analyzed the data of 2 different patient records: SWEDEHEART register and UPMC patient records. In UPMC patient records, we identified patients who had normal fasting blood glucose levels on average 15 days before ST elevation myocardial infarction (STEMI) and checked their fasting blood glucose levels 30 days after STEMI. Omental adipose tissue was collected from patients with or without STEMI through UPMC autopsy program. To investigate the mechanisms behind IR after MI, we induced MI in wild type mice by ligating the coronary artery. We tested insulin sensitivity with an intraperitoneal glucose tolerance test after MI.

Results: We found that 50% of non-diabetic patients (fasting blood glucose levels 99±2.5 mg/ dl) developed hyperglycemia (141±13 mg/dl) after MI, suggesting IR following MI. The mice with coronary ligation had higher IR. Consistently, these mice had higher fasting blood insulin levels and reduced p-Akt in the liver and skeletal muscles. We found that 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, indicating the role of M-CSF in reducing inflammation and maintaining insulin sensitivity. Consistent to this finding, we observed that M-CSF-deficient mice had IR.

Conclusion: Here we show that loss of tissue resident anti-inflammatory CX3CR1-CCR2-VAT macrophages due to diminished M-CSF signaling causes IR.
**Poster: Estrus-cycle dependent variations regulate sensitivity of rat urinary bladder urothelial cells**

**Presenter:** Amanda Wolf-Johnston, Research V

**Research Interest:** Bench (Basic Science)  
Renal-Electrolyte

**Mentors:** Lori Birder PhD

**Funding Source:** NIH

**Authors:** Amanda Wolf-Johnston BSc, Florenta Kullmann PhD, Youko Ikeda PhD, Anthony Kanai PhD, Lori Birder PhD

**Introduction:** A growing body of evidence suggests that symptoms in many chronic pelvic pain syndromes may be influenced by fluctuation in hormones - in particular estrogen (E2). Studies have shown that urinary bladder epithelial (urothelial-UT) cells, which line the bladder lumen, express E2-receptors. In addition, rapid or non-genomic effects of E2 may play a role in release of mediators and/or activation of signaling pathways. The goal of this study was to examine the mechanisms by which E2 alters urothelial sensory functions.

**Methods:** UT cells (UTCs) were cultured from rat urinary bladders using previously described methods in accordance with approval by the University of Pittsburgh Institutional Animal Use and Care Committee. Phosphorylated (p-) p38 expression was examined in whole cell lysates isolated from UTCs or bladder mucosal tissue and subjected to western blotting using a standard protocol. ATP release was examined by collecting effluent following application of chemical stimuli (TRPV1 agonist capsaicin- 10 µM; βE2-100 nM) with or without pretreatment with E2 antagonists. Statistical significance was considered with p < 0.05.

**Results:** Capsaicin evoked ATP was potentiated in the presence of 100nM β-E2 and release was prevented with either Tamoxifen (1µm) or ICI-182,780 (3µm), two esterogenic antagonists. We also find β-E2 increased the expression of (activated) p38 MAPK. The degree to which pp38MAPK expression was increased after β-E2 exposure was linked with estrus cycle. The increase in pp38MAPK was increased in UTC collected from rats in estrus, but not from rats in diestrus or proestrus.

**Conclusion:** Our preliminary findings suggest that estrogens (via beta-receptors) can acutely alter responsiveness of bladder epithelial cells to chemical stimuli. Studies have shown that estrus cycle dependent fluctuations can have profound effects on algogenic mediators and on pain thresholds. Thus, our findings of augmented levels of stress-kinase expression seen in rats in estrus suggest that variations in gonadal hormones may contribute to pain fluctuations in female patients with visceral pain disorders.
**Poster: The regulation of cytochrome b5 reductase 3 on endothelial cell proliferation and lipid metabolism**

**Presenter:** Shuai Yuan, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)  
VMI

**Mentors:** Adam Straub PhD

**Funding Source:** AHA Postdoctoral Fellowship

**Authors:** Shuai Yuan PhD, Megan P. Miller BS, Subramaniam Sanker PhD, Adam C. Straub PhD

**Introduction:** The ability of endothelial cells to proliferate is required for repairing tissue during inflammation and ischemic injury. Nitric oxide (NO) enhances endothelial cell proliferation and ischemic vascular response. Endothelial nitric oxide synthase (eNOS), the primary source of NO in endothelium, is subject to fatty acid mediated modifications (palmitoylation), which allows its correct membrane localization and activation. Notably, lack of fatty acid synthase (FAS) compromises eNOS palmitoylation and membrane association, resulting in reduced cell proliferation. In the liver, cytochrome b5 reductase 3 (Cyb5R3) is critical for fatty acid desaturation and upregulates enzymes including FAS to enhance fatty acid production and elongation. Endothelial Cyb5R3 promotes angiogenesis and protects against ischemic injury by controlling lipid metabolism and NO signaling.

**Methods:** The activity and expression of Cyb5R3 were inhibited by a small molecular inhibitor, ZINC39395747, or lentiviral shRNA. Cell proliferation was evaluated by seeding cells at a low density and crystal violet staining on the following days. Alternatively, cells were allowed to grow confluent for scratch-wound healing assays to determine cell proliferation and migration. Gene expressions of essential enzymes in lipid metabolism were analyzed by quantitative PCR. Cyb5R3 fused with the APEX2 tag was constructed to identify protein interactions with mass-spectrometry. The expression and phosphorylation of eNOS were examined by western blotting. NO availability was measured by the triiodide method following with chemiluminescent detection.

**Results:** Both pharmacological inhibition and gene silencing of Cyb5R3 resulted in impaired endothelial cell proliferation and migration. The Cyb5R3 inhibitor suppressed expressions of fatty acid synthase (FAS), acetyl CoA carboxylase (ACACA/B), glycerol-3-phosphate acyltransferase 1 (GPAM), and carnitine palmitoyltransferase I (CPT1A), which are critical for lipid metabolism, on the mRNA level. Meanwhile, Cyb5R3 knockdown reduced the mRNA of ACACA/B and GPAM, but not FAS and CPT1A. Furthermore, Fatty acid β-oxidation relies on the availability of carnitine. A rate-limiting enzyme synthesizing carnitine, trimethyllysine hydroxylase epsilon, was identified to interact with Cyb5R3. Meanwhile, Cyb5R3 inhibited cells showed decreased phosphorylation of eNOS S1177 and increased phosphorylation basally with reduced NO availability.

**Conclusion:** Cyb5R3 critically regulates endothelial lipid metabolism and NO availability, which can be necessary for normal endothelial cell proliferation.
**Poster:** Four ribosomal proteins regulate CD40 transcription via a disease-associated functional SNP rs6032664 in a complex involving RNA

**Presenter:** Xiaoyu Zhang, Post-Doctoral Associate

**Research Interest:** Bench (Basic Science)
Aging Institute

**Mentors:** Gang Li PhD

**Authors:** Xiaoyu Zhang PhD, Danli Jiang PhD, Yihan Zhao BSc, Yu Yang MD, Qiaoke Gong MD, Gang Li PhD

**Introduction:** Human genetics indicates that CD40, a co-stimulus for B cell activation, is associated with disease susceptibility of multiple aging-related diseases such as cardiovascular diseases, cancers as well as autoimmune diseases. However, the underlying mechanism still remains unknown. Previously, using SNP-seq and FREP-MS, we identified four ribosomal proteins: RPL26, RPL4, RPL8 and RPS9 that specifically bind to the functional SNP (fSNP) rs6032664, one of the four non-coding fSNPs on the disease-associated CD40 locus, suggesting that they potentially function as regulatory proteins modulating CD40 expression via rs6032664.

**Methods:** To prove this hypothesis, in this report, we performed RNAi knockdown on these four proteins in a human B cell line, immunoblotting, real-time PCR and DNA pulldown western blots.

**Results:** We first observed the down-regulation of CD40 expression on both mRNA and protein levels in these knockdown cells. We then demonstrated the specific binding of these ribosomal proteins to rs6032664 by showing an allele-imbalanced binding using a DNA pulldown Western blot. Moreover, we also showed a decreased binding of RPL26 to rs6032664 when we pre-treated the nuclear proteins with both RNase A and RNase R, however, with RNase R showing less effective, suggesting a potential involvement of circRNA in the complex. Furthermore, we showed RPL26 regulating gene expression on both transcriptional and translational level in the human B cell.

**Conclusion:** Together, these data provide evidences that, at least, these four ribosomal proteins are transcription regulators controlling gene expression.
**Poster:** Interrogate the role of IL-17AF and IL-17F in mucocutaneous candidiasis

**Presenter:** Chunsheng Zhou, Graduate Student

**Research Interest:** Bench (Basic Science)  
Rheumatology and Clinical Immunology

**Mentors:** Sarah Gaffen PhD

**Authors:** Chunsheng Zhou BS, Leticia Monin PhD, Jonathan Cohen BS, Erin Childs MS, Rachael Gordon PhD, Mark Shlomchik PhD, Sebastien Gingras PhD, Daniel Kaplan PhD, Sarah Gaffen PhD

**Introduction:** Chronic mucocutaneous candidiasis disease (CMCD) is a chronic fungal infection found in immunodeficient patients with defects in the IL-17A (IL-17) or Th17 pathways, indicating a protective role of IL-17A in anti-Candida immunity. Among the five IL-17-family cytokines, IL-17F shares the most homology with IL-17A at the amino acid level. IL-17A and IL-17F exist as homodimers and also form a heterodimer (IL-17AF). All of these cytokine dimers signal through the same IL-17RA: IL-17RC receptor complex, but the ligands have different binding affinities to the receptor complex (IL-17A > IL-17AF > IL-17F). The biological activities of IL-17A and IL-17F in the context of candidiasis have been well characterized. IL-17A and IL-17F both contribute to immunity to oral and dermal candidiasis, with IL-17A having a more dominant role. However, the contribution of heterodimeric IL-17AF is poorly understood and is hard to determine due to a lack of specific reagents to block only this form of the cytokine. We hypothesized that a dominant negative mutation (IL-17F.S65L) discovered in CMCD patients (Puel et al, Science, 2011) could be a useful tool to interrogate the role of IL-17AF and IL-17F in the immune response against mucocutaneous candidiasis. This mutation impairs binding of IL-17AF and IL-17F to the IL-17 receptor but does not reduce dimerization with either IL-17F or IL-17A. Hence, patients with this mutation had reduced IL-17AF and IL-17F signals but had preserved functional IL-17A. This site (S65L) is highly conserved in mice and other mammalian species.

**Methods:** IL-17F S65L mouse strain was created via CRISPR/CAS9. The expected mutation and potential off-target mutations in the IL-17F S65L mice were screened by DNA sequencing. IL-17F S65L mice were subjected to primary oral and dermal C. albicans infection for 3 days or 5 days. The fungal burden of infected tongues and skin were analyzed by plating the homogenate on agar plate.

**Results:** IL-17F S65L mutant mice were created via CRISPR/Cas9. No off-target issue has been found in the mutant mice. Unlike patients with IL-17F S65L mutation, IL-17F S65L mutant mice were not more susceptible to C. albicans oral and dermal infection than wildtype mice.

**Conclusion:** Our results do not indicate that IL-17AF or IL-17F is necessary for anti-C. albicans immunity.
51-B Poster: Incidence of Postoperative Cognitive Dysfunction in Older Women Undergoing Pelvic Organ Prolapse Surgery

Presenter: Mary Ackenbom, Junior Faculty

Research Interest: Clinical
General Internal Medicine Affiliated

Mentors: Esa Davis MD

Funding Source: American Urogynecology Society PFD Grant; Other

Authors: Mary Ackenbom MD, Esa Davis MD, Meryl Butters PhD, Kaleab Abebe PhD, Lindsey Baranski BS, Halina Zyczynski MD

Introduction: Postoperative cognitive dysfunction (POCD) is transient impairment of memory, concentration, and information processing that is associated with increased morbidity and death. Incidence of POCD after elective noncardiac surgeries is 7-26% and is not well established after pelvic organ prolapse (POP) surgery. Our primary aim was to determine the incidence of POCD 2 weeks post-surgery in women >60 years who underwent POP surgery. We hypothesized that the POCD incidence rate after POP surgery is similar to reported rates of 20% in older persons undergoing non-cardiac surgery.

Methods: A prospective cohort study of 70 women >60 years scheduled for POP surgery. Exclusion criteria included known diagnosis of dementia or cognitive impairment, history of major neurologic disorder, and positive cognitive impairment screen using Modified Mini-mental State Examination. Baseline interviews and data abstraction from medical record provided sociodemographic and clinical factors. Frailty was assessed calculating with the Fried frailty Index. Participants completed questionnaires to assess anxiety, depression, pain, and pelvic floor disorder symptoms, and underwent 8 formal neuropsychological (NP) tests assessing domains of premorbid IQ, memory, executive function, and attention, 2 weeks before and after surgery. Primary outcome: POCD, defined as a decline of $\pm 1$ SD on $\pm 2$ NP tests or a decline of $\pm 2$ SD on $\pm 1$ NP test. Raw scores were transformed to Z-scores (pre to post-testing decline) for each individual NP test to determine participants' POCD status. Chi-squared and Fisher's exact tests used to assess association between POCD and clinical factors.

Results: Seventy women were enrolled and completed pre- and postoperative NP testing. Preliminarily, median age was 70 (interquartile range (IQR) 68-74). Median years of education was 13 (IQR 12–16). Premorbid IQ scores were average to above-average compared to the general population at 103.6±13.3 (mean±SD). POCD incidence rate was 26%. POCD was associated with more subjective hearing loss ($p<0.05$) and greater use of inhalational anesthetic gas ($p<0.05$). Factors associated with POCD ($p<0.02$) included older age, less education, lower premorbid IQ and more anticholinergic medication use. Frailty status ($p=0.308$) and duration of anesthesia ($p=0.269$) were not associated with POCD.

Conclusion: The 26% POCD rate in this cohort is consistent with POCD rates in published reports. Preoperative counseling should include review of POCD as a possible outcome after these elective surgeries. Future research will study the longitudinal course of POCD in this patient population over 1 year.
52-B **Poster:** Correlating the Oral Microbiome with Nitrate Metabolism in Patients with PH-HFpEF

**Presenter:** Noel Britton, Graduate Student

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** This abstract is funded by: 5P01HL103455-08

**Authors:** Noel Britton MPH, Carl Koch MD, Andrea Levine MD, Nicole Helbling, Sruti Shiva PhD, Adam Fitch MS, Rachel Nettles MS, Marc Simon MD, Barbara Methe PhD, Mark Gladwin MD, Alison Morris MD

**Introduction:** In humans, commensal oral bacteria reduce nitrate to nitrite, which is ultimately further reduced to nitric oxide (NO), a potent vasodilator. Evidence suggests that microbial bioactivation of nitrate may play a role in the prevention and treatment of systemic vascular pathology and pulmonary hypertension (PH). To date, no studies have examined the association between alterations in the ability to reduce nitrate to nitrite, the oral microbiome, and hemodynamics in patients with PH-HFpEF. The objective of this study is to determine differences in conversion of oral nitrate to nitrite in patients with PH-HFpEF and controls.

**Methods:** Controls and patients with PH-HFpEF (mean PAP = 25 mm Hg, PCWP > 15 mm Hg, TPG>=12, cardiac index >2.0 L/min/m2 on clinical right heart catheterization) were administered 1000mg of sodium nitrate orally. Plasma nitrate and nitrite were measured at baseline and at 2- and 6-hours following drug administration. Saliva, stool and tongue scraping samples were collected before nitrate administration for bacterial DNA extraction. We amplified the V4 hypervariable region of the 16s rRNA gene for sequencing on the Illumina MiSeq platform.

**Results:** Baseline (PH-HFpEF 78.28um vs Control 106.23um, p=0.14), 2-hour (PH-HFpEF 401.16um vs Control 648.31um, p=0.32), and 6-hour (PH-HFpEF 545.83um vs Control 340.11um, p=0.25) plasma nitrate levels were similar in patients with PH-HFpEF (n=2) and healthy controls (n=3). Baseline plasma nitrite levels were also not significantly different in controls and patients with PH-HFpEF (PH-HFpEF 0.08um vs Control 0.10um, p=0.64). Post-oral nitrate administration, plasma nitrite levels increased in controls, but remained unchanged in PH-HFpEF patients at 2 hours post oral nitrate administration (PH-HFpEF 0.17um vs Control 0.96um, p=0.03) and 6 hours post administration (PH-HFpEF 0.16um vs Control 0.70um, p=0.05).The taxonomic compositions of bacterial communities sampled on the tongue were significantly different between patients with PH-HFpEF and healthy controls (weighted Unifrac p-value=0.03. On the tongue, patients with PH-HFpEF tended to have lower abundance of known nitrate reducing bacteria (p=0.16). In saliva samples, there were trends toward taxonomic differences between patients with PH-HFpEF and controls (weighted Unifrac p-value=0.15). However, patients with PH-HFpEF were found to have significantly higher abundance of known nitrate reducing bacteria including Rothia, Prevotella and Streptococcus in saliva samples compared to controls (p=0.03).

**Conclusion:** In a pilot study of nitrate reduction in PH-HFpEF, we found a diminished ability to reduce nitrate to nitrite as measured by plasma levels after oral nitrate administration. Further studies may provide insight into whether variations in the microbiome contributes to the pathobiology of PH-HFpEF and suggest novel therapeutic possibilities.
**Poster: A randomized pilot trial of home-based physical activity plus dietary intervention to improve physical function in patients with advanced liver disease**

**Presenter:** Hui-Wei Chen, Clinical Fellow

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

**Mentors:** Andres Duarte-Rojo MD

**Authors:** Hui-Wei Chen MD, Arny Ferrando PhD, Margaret Pauly MS, Thaddeus Bartt MD, Michael A. Dunn MD, W. Ray Kim MD, Andres Duarte-Rojo MD

**Introduction:** Frailty is highly prevalent and a poor prognostic factor in patients with cirrhosis. Multiple prehabilitation programs have been proposed to prevent frailty in order to improve clinical outcomes, however, few patients have access to specialized training centers to make these programs practical and generalizable. A randomized pilot trial was performed to study the benefits of a home-based physical activity program (PAP) in patient with cirrhosis.

**Methods:** Patients with cirrhosis referred for liver transplantation evaluation at a tertiary hospital were invited to participate. Patients were given a physical activity tracker (Fitbit; San Francisco, CA) and their activities remotely monitored (Fitabase; San Diego, CA) for 14 weeks with the first 2 weeks being the trial-run period. At the end of week 2, eligible patients were randomized to an active (PAP) or control group. All patients received a dietary intervention including 11 g/d of an essential amino acid supplementation (Armada Nutr.; Spring Hill, TN). PAP consisted of biweekly educational and counseling sessions to discuss home-based opportunities to increase daily physical activity and to establish daily step count goals for each period. 6-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET) were used to assess changes in aerobic fitness.

**Results:** Twenty patients with cirrhosis (60% male; mean age: 55 ± 9 years old) and MELD 15 ± 3 were prospectively enrolled. Three patients were eliminated prior to randomization, and 17 were eventually randomized (9 to active group). There were no significant differences in the initial MELD-sodium (MELD-Na) score between active and control group (16 ± 4 and 18 ± 3, respectively; p=0.16). There were also no significant differences in changes in MELD-Na score for each group against its respective baseline by the end of the study (active group: 14 ± 4, p=0.37; control group: 19 ± 5, p=0.47). At baseline, 9 (53%) patients were sedentary performing <2500 steps/day. Comparing poorest and best 2-week performance periods to baseline, exercise group had a proportional change in daily steps of -8% and 58%, contrasting the control group at -45% (p=0.03) and 28% (p=0.29), respectively. The 6MWT showed a trend for improvement in the PAP group by the end of the study (baseline 423±26 m vs. 482±35 m) while the controls had a non-significant drop (baseline 418±26 m vs. 327±74 m), for a significance between groups difference. CPET did not change significantly in either PAP or control group.

**Conclusion:** The home-based PAP was successful in maintaining physical performance among patients with cirrhosis, and it improved aerobic fitness according to 6MWT but not to CPET. Our data support the use of home-based prehabilitation programs with physical activity trackers monitoring for liver transplant candidates.
Poster: Towards understanding of exercise intensity in patients with end-stage liver disease: an insight into heart rate and activity monitoring with physical activity trackers

Presenter: Hui-Wei Chen, Clinical Fellow

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Andres Duarte-Rojo MD

Authors: Hui-Wei Chen MD, Arny Ferrando PhD, Michael A. Dunn MD, W. Ray Kim MD, Andres Duarte-Rojo MD

Introduction: Exercise should be of a minimum intensity to result in physiologic adaptation. Moderate-intensity exercise is recommended but there are no guidelines on its definition in end-stage liver disease (ESLD). Among the various methods to estimate intensity, heart rate reserve (%HRR), based on the percentage increase from resting to maximal HR, is frequently used. However, %HRR might be challenging in ESLD given its hyperdynamic circulation. We aimed to test agreement between %HRR, cadence method (steps/minute), and a proprietary algorithm in ESLD patients monitored with physical activity trackers.

Methods: Twenty ESLD patients (60% male; age 55±9, MELD 15±3, beta-blockage 30%) were given a physical activity trackers (Fitbit) to monitor HR and steps/day for 14 weeks, as part of a randomized clinical trial. We calculated %HRR as HRmax/peak–HRrest x %desired intensity, using following categories: very light activity <30%, light 30-39%, moderate 40-59, vigorous-to-maximal =60%. HRmax/peak was defined as 220–age, and HRrest was obtained at 6:00 AM±30-min, from 11 consecutive stable HR readings. We classified cadence as follows: sedentary-to-very light 0–39 (steps/min), light 40-79, moderate 80-130, and vigorous >130. Agreement between exercise intensity methods for the 14-week period, and change in exercise intensity from 2-week baseline to periods of maximum or minimum activity were tested (=1% difference in =moderate activity was considered clinically relevant, as this change corresponds to =15 minutes/day of such intensity).

Results: Over 1.75 million HR determinations collected by Fitbit were analyzed. The three exercise intensity methods significantly differed when compared against each other, with highest agreement between Fitbit algorithm and cadence (93%, kappa=0.46;p<0.001), intermediate between %HRR and cadence (89%, kappa=0.21;p<0.001), and lowest between Fitbit and %HRR (85%, kappa=0.31;p<0.001). The period of maximum activity was characterized by a significant >800 steps/day increase when compared to baseline, whereas the period of minimum activity showed a >2300 steps/day decrease. Against maximum activity, cadence was able to identify a 1.16% difference, however, HRR (0%) and Fitbit (-0.24%) did not. For minimum activity, cadence (-1.78%) and Fitbit (-1.23%) detected a difference, whereas HRR did not (0.34%).

Conclusion: Not surprisingly, %HRR did not mirror exercise intensity given the particular cardiovascular physiology of ESLD (increased basal heart rate, beta-blockers use, and chronotropic incompetence). Cadence showed better agreement and represented changes in physical activity. However, in the absence of a standard of reference we cannot be conclusive on its superior role as an intensity marker. Rates of perceived exertion need to be included in future studies.
56-B Poster: Humoral Immunity in End-Stage Lung Disease Prior to Lung Transplantation

Presenter: Kara Coffey, Clinical Fellow

Research Interest: Clinical Pulmonary, Allergy and Critical Care Medicine

Mentors: Andrej Petrov MD

Funding Source: Investigator-initiated w/ support from CSL Bering

Authors: Kara Coffey MD, Russell Traister MD, Maylene Xie MD, Joseph Pilewski MD, Andrej Petrov MD

Introduction: Hypogammaglobulinemia (HGG) has been reported in more than 60% of lung transplant (LT) recipients and decreased pneumococcal titers (< 70% protective titers) have been reported in 86% of LT recipients following lung transplantation. We evaluated humoral immunity in subjects with end-stage lung disease prior to lung transplantation.

Methods: This is a single center prospective observational study of LT recipients. Pre-transplant IgG levels and pneumococcal titers were obtained within one year prior to transplant. Analysis was performed using non-parametric tests.

Results: 94 subjects were prospectively evaluated. The median age was 60 years (IQR, 51-64); 63.8% male and 90% Caucasian. 41.5% of subjects had idiopathic pulmonary fibrosis (IPF) and 25.5% had chronic obstructive pulmonary disease (COPD). HGG was present in 15% and decreased pneumococcal titers were present in 73% of subjects. Immunoglobulin levels were lower in subjects with COPD compared with other diseases (p=0.0002). HGG (IgG < 700 mg/dl) occurred in 33.3% of COPD subjects and 2.6% of IPF, with no inter-group difference in the number of protective pneumococcal titers (p=0.65). Subjects with lower pre-transplant IgG had fewer protective pneumococcal titers (p=0.001), and pre-transplant prednisone dosing was inversely correlated with pre-transplant IgG levels (Spearman’s rho= -0.25, p=0.01) and less than 2 protective pneumococcal titers (p=0.005). Pre-transplant IgG levels were higher in those with CT scan-confirmed bronchiectasis.

Conclusion: The type of underlying end-stage lung disease and prednisone dosing contribute to HGG and prednisone dosing impacts pneumococcal antibody titers. The presence of bronchiectasis is not associated with HGG in end-stage lung disease.
Poster: The Association of Sleep Apnea with Invasive Cardiopulmonary Hemodynamics

Presenter: Michael Genuardi, Clinical Fellow

Research Interest: Clinical Cardiology

Mentors: Sanjay Patel MD MS

Funding Source: T32

Authors: Michael Genuardi MD, Rachel Ogilvie PhD MPH, Adam Handen MS, Marc Simon MD MS, Jared Magnani MD MS, Stephen Chan MD PhD, Sanjay Patel MD MS

Introduction: Sleep apnea increases pulmonary artery pressure at night, but whether sleep apnea causes persistent daytime pulmonary hypertension is less clear.

Methods: Adults who underwent an overnight sleep study within our large health care system between 3/1999 and 12/2017 were eligible for inclusion if they also underwent native right heart catheterization up to 1 year prior or 3 years after the sleep study. Apnea hypopnea index (AHI) was extracted from sleep study reports and used to classify sleep apnea as absent, mild, moderate or severe. History of hypertension, diabetes, and atherosclerosis was obtained from the medical record by query of ICD-9 and -10 diagnostic codes. Atherosclerosis was defined as any of: ischemic heart disease, cerebrovascular disease or peripheral arterial disease. The primary outcomes were catheterization parameters: mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR) and cardiac output (CO). Parameters were compared across categories of sleep apnea severity. Associations were then examined continuously with linear regression to assess the relation between AHI and hemodynamics, with adjustment for confounding by age, sex and BMI.

Results: A total of 820 patients were identified meeting inclusion criteria and included. The mean ± SD of AHI was 24.8 ± 27.1 events/hr. Patients with more severe sleep apnea were older, more likely to be male, had higher BMI and had a higher prevalence of hypertension, diabetes and atherosclerotic disease than patients with less severe sleep apnea. Accounting for confounding by age, sex and BMI, each 10-unit increase in AHI corresponded to 0.4 mmHg higher PCWP (95% CI 0.2, 0.6), but no meaningful change in mPAP (0.2 mmHg, 95% CI 0.2, 0.6). AHI was not associated with a significant change in PVR (-0.04 Woods units per 10-unit AHI, 95% CI -0.10, 0.03) or CO (-0.01 L/min per 10-unit AHI, 95% CI -0.06, 0.03).

Conclusion: In this large, retrospective analysis, sleep apnea severity was associated with common cardiovascular comorbidities and elevated PCWP, but not elevated mPAP. Sleep apnea may not be associated with clinically important persistent daytime pulmonary hypertension.
**Poster: The OPTIFAST Very Low Calorie Diet (VLCD) Results in Type 2 Diabetes Remission**

**Presenter:** Evan Keller, Medical Student

**Research Interest:** Clinical Endocrinology and Metabolism

**Mentors:** David Rometo MD

**Funding Source:** NIH T35

**Authors:** Evan Keller BS, David Rometo MD, Emily Timm MS, Katrina Han MD

**Introduction:** A Very Low Calorie Diet (VLCD) using meal replacements has been shown to achieve Type 2 Diabetes (T2DM) remission. This is a retrospective analysis of a VLCD used in a clinical obesity medicine setting. We hypothesized that completion of a 6 month OPTIFAST VLCD program and Weight Loss (WL) % would be positively associated with markers of T2DM control and remission.

**Methods:** Baseline and 6 month values for weight, HbA1c, # daily injections (DI), and T2DM medications were collected. Patients were stratified into 3 categories of final weight loss (<14.9% - group 1, 15-24.9% - group 2, and >25% - group 3), and 4 categories of T2DM control – complete remission (A1c <5.7, no DM meds), partial remission (A1c <6.5, no DM meds), euglycemia (A1c <5.7 on DM meds), and controlled (A1c <6.5 on DM meds).

**Results:** We evaluated 42 patients who had T2DM at baseline. In 28 patients on injectable medications, mean DI decreased from 2.75 to 0.96 (p<0.0001). Mean A1c decreased from 7.69 to 5.99 (n=42, p<0.0001). 6 month A1c was 6.34 in group 1, 5.89 in group 2 and 5.46 in group 3 (n=42, p<0.05). 3 achieved complete remission, 5 partial remission, 13 euglycemic, and 12 controlled. 20 were on insulin at baseline, 10 on insulin at 6 months. TDD of insulin was 95.2+/−70.414 at baseline, and 18 units +/- 24 at 6 months (P<.0001).

**Conclusion:** Program completion resulted in T2DM control and remission, and both more pronounced with increased % WL.
**Introduction:** Renal biopsy is the gold standard for diagnosis of lupus nephritis (LN). Findings of specific LN classes, activity and chronicity indices on renal biopsy are used to help guide therapy. It is unclear whether clinical biomarkers change and how quickly they occur after biopsy-confirmed LN. Therefore, the aims of this study were: 1) to determine whether creatinine (Cr), proteinuria, and hematuria improve at 12 months after renal biopsy; 2) to determine whether lupus clinical biomarkers (C3/C4, dsDNA Ab, ESR, CRP) change over 12 months; and 3) to compare biomarker changes among different LN classes.

**Methods:** Using the University of Pittsburgh Health Sciences Tissue Bank (HSTB) and Renal Pathology Department stored biopsy specimens, we identified 37 cases of LN from 2010-2016. Using the electronic database, we obtained LN classes and biomarkers checked within a month before and 12 months after biopsy date for each sample. Descriptive analyses summarized the changes in biomarkers from time of biopsy to 12 months afterward.

**Results:** Of the 37 LN cases, 31 had baseline Cr values at time of biopsy and 29 had Cr values at 12 months after biopsy. In LN class III-IV (n=14), mean Cr decreased from 2.13 to 1.35. In LN class V either isolated or combined with other LN classes (n=13), mean Cr remained stable from 1.52 to 1.51. In isolated LN class V (n=4), mean Cr remained stable from 0.89 to 0.94. At 12 months, urine RBC (n=12) decreased or remained stable in all but four, and urine protein/Cr ratio (n=3) decreased in all. At 12 months, C3 and C4 (n=20) both increased in 11 (55%), with the other cases having either C3 or C4 increased while the other complement decreased or unchanged. DsDNA Ab (n=18) decreased in all but one; ESR (n=11) decreased in all but one; and CRP (n=11) decreased in all but three.

**Conclusion:** These findings suggest that 12 months after renal biopsy diagnosis of LN, clinical biomarkers improved in the vast majority of cases. Renal function improved in class III-IV LN and remained stable in the rest. Proteinuria and hematuria decreased at 12 months. C3/C4 increased, and dsDNA Ab, ESR, and CRP decreased in the majority. These findings suggest that findings obtained from renal biopsy helped guide therapy in LN and led to improved clinical biomarkers at 12 months. Further studies are needed to determine what factors contributed to improvement in clinical biomarkers over time after renal biopsy.
**Poster: Safety and Efficacy of Direct Oral Anticoagulants Versus Warfarin in Chronic Kidney Disease**

**Presenter:** Amber Makani, Clinical Fellow

**Research Interest:** Clinical Cardiology

**Mentors:** Suresh Mulukutla MD

**Authors:** Amber Makani MD, Suresh Mulukutla MD, Samir Saba MD, Aditya Bhonsale MD, Michael Sharbaugh MPH, Floyd Thomas BS, Yisi Wang MPH, Oscar Marroquin MD, Joon Lee MD

**Introduction:** Approximately one in five patients with chronic kidney disease has been found to have symptomatic atrial fibrillation. In addition, 50% of patients with atrial fibrillation have some degree of renal dysfunction. While the risk of stroke in patients with atrial fibrillation or chronic kidney disease are higher than that of the general population, the presence of concomitant disease has been found to have an even higher risk of stroke and greater mortality. Although atrial fibrillation and chronic kidney disease often coexist in the same patient population, recommendations with regard to anticoagulation in this population is still highly debated. Due to the increased risk of hemorrhagic events in patients with renal dysfunction, including hemorrhagic stroke, intracerebral bleeding and gastrointestinal bleeding, patients with CKD were excluded from phase III trials investigating the use of direct acting oral anticoagulants (DOAC) in patients with atrial fibrillation. Despite lack of FDA labeling for use of DOACs in patients with a CrCl <30, use of these agents for stroke prevention is becoming increasingly common. There has been a call from both national cardiology and nephrology groups for more data to address the safety and efficacy of anticoagulation in patients with CKD.

**Methods:** We included patients who were >;18 years old who had non-valvular atrial fibrillation and CHA2DS2-VASc score >2 who were treated with anticoagulation from a single-center, multi-site healthcare system. We evaluated outcomes including mortality, ischemic strokes, and bleeding events in this population and stratified patients by treatment with DOAC versus warfarin across ranges of CKD.

**Results:** There were 21,733 patients with a CHA2DS2-VASc score of > 2 included in this analysis. Compared with warfarin, DOAC use in patients with impaired renal function was associated with lower risk of mortality with a hazard ratio [HR]: 0.76 (95% confidence interval [CI] 0.70-0.84, p-value <0.001) in patients with eGFR>60, HR 0.74 (95% CI 0.68-0.81, p-value <0.001) in patients with eGFR>30-60, and HR 0.76 (95% CI 0.63-0.92, p-value <0.001) in patients with eGFR<30 or on dialysis. Bleeding requiring hospitalization was also less in the DOAC group with a HR 0.93 (95% CI 0.82-1.04, p-value 0.209) in patients with eGFR>60, HR 0.83 (95% CI 0.74-0.94, p-value 0.003) in patients with eGFR>30-60, and HR 0.69 (95% CI 0.50-0.93, p-value 0.017) in patients with eGFR<30 or on dialysis.

**Conclusion:** In patients with concomitant renal impairment and atrial fibrillation, DOAC use was associated with lower risk of bleeding events and all-cause mortality when compared to warfarin. This apparent benefit was observed in all stages of renal impairment including those patients on dialysis.
61-B Poster: Obstetric and Cardiovascular Outcomes in Pregnant Women with Hypertrophic Cardiomyopathy: A National Cohort Study

Presenter: Ahmad Masri, Post-Doctoral Scholar

Research Interest: Clinical Cardiology

Mentors: Timothy Wong MD

Funding Source: T32

Authors: Ahmad Masri MD, Jenna Skowronski MD, Malamo Countouris MD, Michael Genuardi MD, Kathryn Berlacher MD, Steve Caritis MD, Steven Reis MD, Timothy Wong MD

Introduction: Hypertrophic cardiomyopathy (HCM) is common in women of child-bearing age. We sought to compare obstetric (OB) and cardiovascular (CV) outcomes of encounters of pregnant women with HCM vs healthy women vs left ventricular hypertrophy (LVH).

Methods: We leveraged the Nationwide Readmission Databases (January 2010 through August 2015), to identify encounters of pregnant women (18-40 years of age) who are 1) healthy without associated comorbidities 2)HCM and 3)LVH. Outcomes were unmatched and matched (2:1) OB (composite of pre-eclampsia, post-partum hemorrhage, and gestational hypertension) and CV (composite of in-hospital mortality, heart failure, acute coronary syndrome and pulmonary embolism).

Results: There were 12,662,090, 368, and 1960 encounters for healthy, HCM, and LVH pregnant women, respectively. In healthy vs HCM vs LVH, median length of stay was 2 days (2-3) vs 3 days (2-3) vs 4 days (3-6), and prevalence of C-section was 29% vs 45% vs 64% (all p<0.0001). unmatched OB outcomes occurred in 8% of healthy vs 11% of HCM (p=0.2) vs 33% of LVH (p<0.0001 for all). Unmatched CV outcomes occurred in 0.008% of healthy vs 5% of HCM vs 5% of LVH (p<0.0001). In-hospital mortality was rare across all groups (none in HCM). Matched health:HCM OB and CV outcomes were similar, while matched healthy:LVH showed worse OB and CV outcomes in LVH.

Conclusion: Pregnant women with HCM had worse CV outcomes but similar OB outcomes when compared to healthy women. Strategies to reduce CV events in women with HCM and LVH are needed.
62-B Poster: Readmissions in Patients Undergoing Percutaneous Coronary Intervention Stratified by Access Site

Presenter: Ahmad Masri, Post-Doctoral Scholar

Research Interest: Clinical Cardiology

Mentors: Suresh Mulukutla MD

Funding Source: T32

Authors: Ahmad Masri MD, Michael Sharbaugh MPH, Mourad Senussi MD, Andrew Althouse PhD, Amanda Malecky BS, Floyd Thoma BS, Amr Barakat MD, Catlin Toma MD, Conrad Smith MD, John Schindler MD, Joon Lee MD, Suresh Mulukutla MD

Introduction: Trials have shown improved survival with trans-radial access (TRA) over trans-femoral access (TFA) in patients undergoing percutaneous coronary intervention (PCI). We sought to evaluate readmissions and potential mechanisms of improved outcomes in patients undergoing PCI stratified by access site.

Methods: 12,902 patients underwent PCI (2011-2017) in three hospitals. We excluded patients receiving mechanical support (n=361), prior CABG (n=2,870), re-intervention (n=1,743), unconventional anticoagulation (n=33) and no follow-up (n=128). Outcomes (adjusted and matched) were all-cause readmissions, bleeding readmissions, venous thromboembolism (VTE) readmissions and all-cause mortality. We used 26 variables for adjusted Cox-Proportional Hazard models and to create a 1:1 matched cohort.

Results: 7,799 patients were included (66.6±12.3, females 35%); 1,910 (25%) underwent PCI via TRA. The prevalence of TRA increased from 4% in 2011 to 50% in 2017. In TRA vs TFA, 1-year outcomes included: all-cause readmission (5.5% vs 7.3%, HRadjusted 0.88, 95% CI 0.80, 0.96, p=0.005), bleeding readmission (2.9% vs 4.1%, HRadjusted 0.84, 95% CI 0.65, 1.08, p=0.170), VTE readmissions (0.4% vs 1.1%, HRadjusted 0.70, 95% CI 0.42, 1.16, p=0.164), and all-cause mortality (5.5% vs 7.3%, HRadjusted 0.97, 95% CI 0.83, 1.14). In the 1:1 matched cohort, there were 1,839 patients in each group. There was no association between TRA use and improved outcomes.

Conclusion: Readmissions are common post PCI and are potentially more prevalent post TFA PCI. Bleeding events were driven by non-access site bleeding, VTE episodes were not different by access site, and all-cause mortality was not different. The mechanism of improved mortality through TRA remains to be elucidated.
63-B Poster: Frequent Discordance Between Etravirine Phenotype & Genotype in Subtype C ART Failure

Presenter: Kevin McCormick, Post-Doctoral Associate

Research Interest: Clinical Infectious Diseases

Mentors: John Mellors MD

Funding Source: The Bill and Melinda Gates Foundation.

Authors: Kevin McCormick PhD, Kerri Penrose MS, Chanson Brumme PhD, Richard Harrigan PhD, Raquel Viana PhD, John Mellors MD, Urvi Parikh PhD, Carole Wallis PhD

Introduction: Etravirine (ETR) is a second-generation NNRTI that is used as a component of combination ART for treatment-experienced persons. The extent of cross-resistance between nevirapine (NVP) and efavirenz (EFV) and ETR is not well defined especially in low and middle-income countries (LMIC) where switches from first-line ART may be delayed. To address this gap, we investigated the susceptibility to ETR of subtype C HIV-1 among individuals on failing first-line NNRTI-containing regimens in South Africa (SA) and compared ETR phenotype to genotype.

Methods: Recombinant HIV-1-LAI containing bulk-cloned full-length RT amplified from plasma from 100 HIV-1 subtype C-infected individuals failing first-line ART (>10000 cp/ml and >1 NNRTI RAM) were phenotyped for ETR susceptibility in TZM-bl cells. Fold-change was calculated using a composite IC50 from 12 treatment-naïve individuals from SA. Genotypic scores (Stanford HIVdb v8.4) were categorized as partial or complete discordance if deviated from phenotype clinical cut-offs (DUET trials) by one or two tiers respectively. Correlations were determined using Pearson's coefficient (r). WT reversions of K65 were made in clonally isolated plasmids with the QuickChange II Site-Directed Mutagenesis Kit.

Results: Of 100 first-line ART failures, 55 had reduced ETR susceptibility above the clinical cut-off of 2.9-fold higher than the control IC50. The fold-change (FC) did not strongly correlate with genotypic score (r=0.47) with 44% of samples partially and 4% completely discordant. Of the 33 samples with FC>10, 26 samples were categorized as 'low' or 'intermediate' resistant by the HIVdb (Figure). The ETR-associated mutations L100I, Y181C and/or M230L were present in 79% (26/33) of samples with FC>10 but only in 4% (2/46) of samples with a FC<2.9. By contrast, the HIVdb NNRTI mutations A98G, K101H, E138A/K, V179D, Y188L, G190A, H221Y and P225H did not correlate with ETR resistance. The NRTI mutation 65R was associated with ETR resistance but reversion to 65K had no effect on ETR susceptibility. Rather, 65R was a marker of more prolonged ART failure and the accumulation of NNRTI mutations that conferred ETR resistance.

Conclusion: Phenotypic cross-resistance to ETR is common in first-line NNRTI-containing ART failure in SA. Genotype-based algorithms differentially classify ETR susceptibility in Subtype C. More appropriate weighting of combinations of ETR associated mutations is needed to improve genotype prediction of ETR phenotype.
Poster: Relationship between Gait Speed, Arterial and Cardiac Stiffness, and Cerebral Amyloid-β Deposition and Cerebral Blood Flow in Healthy Older Adults

Presenter: Neelesh Nadkarni, Junior Faculty

Research Interest: Clinical Geriatric Medicine

Funding Source: K23

Authors: Neelesh Nadkarni MD, PhD, FRCPC, Subashan Perera PhD, Emma Barinas-Mitchell PhD, Steven DeKosky MD, William Klunk MD, PhD, Oscar Lopez MD

Introduction: Slower gait is associated with greater cerebral amyloid-β (Aβ) deposition, a key component of Alzheimer’s disease (AD) pathology, and Aβ is associated with increased arterial stiffness. Whether gait speed is associated with cardiac and arterial stiffness, and cerebral blood flow (CBF) is unknown. We examined the cross-sectional association between gait speed, Aβ, CBF, and cardiac and arterial stiffness in cognitively normal (CN) older adults.

Methods: We assessed gait speed on 15’ walk, cerebral Aβ on Pittsburgh-B PET as standardized uptake value ratio (PiB SUVR), CBF on arterial spin labeling MRI, cardiac stiffness on QRS voltage on EKG, and arterial stiffness using carotid-femoral pulse-wave velocity (cf-PWV). Statistical methods included Pearson’s correlations, regression, and path analysis.

Results: In this population (N=50, 86±3 years), gait speed correlated with global PiB SUVR (r=-0.30, p=0.035), global CBF (r=-0.32, p=0.029), cf-PWV (r=-0.30, p=0.037) and QRS voltage (r=0.34, p=0.016). Gait speed was associated with QRS voltage (β=0.35, p=0.013), cf-PWV (β=0.28, p=0.048), PiB SUVR (β=-0.27, p=0.06) and CBF (β=-0.33, p=0.026). The association between gait speed and QRS voltage remained significant (β=0.36, p=0.007) despite adjustment for age, gender, BMI and hypertension. Path analysis revealed that arterial stiffness had a significant indirect effect on slower gait through greater amyloid-β deposition (β=0.31, p<0.05) but not through lower CBF or reduced QRS voltage; however, slower gait was influenced by higher CBF (β=-0.25, p<0.05) and lower QRS voltage (β=0.33, p<0.05).

Conclusion: Slow gait may be associated increase in Aβ deposition, and with cardiac and arterial stiffness. Greater arterial stiffness may contribute to slow gait by influencing AD pathology, independent of cardiac stiffness. The relationship between higher CBF and slower gait remains unclear.
**Poster: Lung Tissue Bacterial Communities Vary By Patient But Not By Anatomical Lobe Sampled In End-Stage Idiopathic Pulmonary Fibrosis: The Microbiome In Lung Explants Study (Miles-IPF)**

**Presenter:** Rachel Nettles, Research III

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** K23

**Authors:** Rachel Nettles MS, Georgios Kitsios MD, Spencer Winters MD, John Sembrat, Daniel Kass MD, Libing Yang MDc, Xiao-Hong Wang MS, Shulin Qin MD, Adam Fitch MS, Kathleen Lindell PhD, Barbara Methe PhD, Bryan McVerry MD, Mauricio Rojas MD, Alison Morris MD

**Introduction:** Lung microbiome profiles characterized by bronchoscopic sampling in patients with early idiopathic pulmonary fibrosis (IPF) have been associated with disease progression and mortality. The anatomical sites of the resident microbiota and the community profiles in end-stage IPF have not been defined. We sought to characterize the regional lung tissue microbiome in patients with end-stage IPF in the Microbiome in Lung Explants Study (Miles-IPF).

**Methods:** We obtained lung tissue specimens from explanted organs at the time of lung transplantation or autopsy from patients with IPF, cystic fibrosis (CF), chronic obstructive lung disease (COPD), and donor lungs rejected for transplant (Control). To assess for possible spatial heterogeneity of microbial communities in IPF, we sampled three sites (lower, right-middle or lingula, and upper lobe) per patient. From each tissue sample, we extracted genomic DNA and amplified and sequenced the V4 region of 16S rRNA gene on the Illumina MiSeq platform per established protocols.

**Results:** We analyzed explants from 66 IPF patients (29 with multi-lobar sampling), 20 Control lungs, 20 CF and 20 COPD patients. Basilar samples from IPF lungs had much lower bacterial loads (median 16S reads: 894 [interquartile range: 1,969]) and different taxonomic composition (Permanova p-value for Bray-Curtis dissimilarity <0.001) compared to basilar samples from CF (median 16S reads: 11,760 [16,180], p<10^-4) and Control lungs (median 16S reads: 12,390 [17,172], p<10^-4). Low bacterial loads in IPF patients were demonstrated across all three lobes in patients with multi-lobar sampling, with the notable exception of five (14%) patients who showed consistently high bacterial loads in all regions (median 16S reads: 18,023 [3,597]). IPF patients with high bacterial loads were more likely to have died than undergone lung transplantation compared to patients with low bacterial loads (p=0.03). Taxonomic composition of communities did not vary by anatomic lobe sampled in IPF lungs but was markedly different between patients with high vs. low bacterial loads (Permanova p-value = 0.001) regardless of lobe sampled.

**Conclusion:** In a case-control study of lung explants, IPF lungs revealed low biomass bacterial communities without evidence of spatial heterogeneity across the apico-basilar gradient of fibrosis. A subgroup of patients who were more likely to have died than to undergo lung transplantation exhibited high bacterial loads and taxonomic similarity across all lobes. With such evidence of patient-specific (and not lobe-specific) heterogeneity in the lung microbiome of IPF, personalized medicine approaches for microbiome-targeted interventions in IPF are needed.
**Poster Abstracts**

**66-B Poster:** Metagenomic sequencing of respiratory microbial communities for detection of etiologic pathogens of pneumonia in mechanically-ventilated adult patients

**Presenter:** Rachel Nettles, Research III

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** K23

**Authors:** Rachel Nettles MS, Libing Yang MDc, Barbara Methe PhD, Shulin Qin MD, Adam Fitch MS, John Evankovich MD, William Bain MD, Daniel Dunlap MD, Faraaz Shah MD, Sarah Rapport MPH, Janet Lee MD, Alison Morris MD, Bryan McVerry MD, Justin O'Grady MD, Georgios Ki

**Introduction:** Metagenomic sequencing of respiratory microbial communities has shown promise for developing novel pneumonia diagnostics needed to overcome the well-appreciated limitations of the current culture-based diagnostic paradigm. However, the high human:microbial DNA ratio (>99:1) in respiratory specimens makes clinical metagenomics challenging for direct-from-sample, culture-independent applications. Thus, we examined the technical feasibility and clinical validity of metagenomic sequencing with the rapid turnaround MinION nanopore sequencing device (Oxford Nanopore Technologies) using a microbial DNA enrichment pre-processing step.

**Methods:** We enrolled mechanically-ventilated patients with clinical suspicion of pneumonia and collected endotracheal aspirate (ETA) samples within 48hrs of intubation. We applied a saponin-based method for human DNA depletion, quantitatively assessed by the relative change in qPCR signal of a human reporter gene (GADPH) compared to microbial 16S rRNA gene in depleted vs. undepleted control samples. We performed nanopore metagenomic sequencing and identified microbial species with the “What’s In My Pot” (WIMP) software. We compared nanopore results (number of reads of highly abundant respiratory pathogens) against clinical respiratory culture results and standard 16S rRNA (16S) gene profiles sequenced using the Illumina MiSeq.

**Results:** We enrolled 14 patients, of whom six (43%) had positive respiratory specimen cultures for pathogens. Successful microbial DNA enrichment in ETA samples (~1000-fold reduction of human DNA) allowed for sequencing of high numbers of microbial reads in infected samples (median 5,987, range 1,209-80,739) with nanopore. Nanopore, 16S and culture results were concordant in 10/14 (71%) cases: in four culture-positive cases, both sequencing approaches showed high abundance of taxa/species corresponding to the clinical isolates, and in six culture-negative cases no abundance of respiratory pathogens was found by both sequencing methods. Discordant results were found for two cases of clinical S. aureus pneumonia, where nanopore and 16S showed only a trace signal of S.aureus, and in two culture-negative cases, when nanopore sequencing suggested potentially missed pathogens (i.e. E.coli and H. influenza, respectively).

**Conclusion:** In this study, we demonstrate technical feasibility and proof-of-concept clinical validity for the detection of culprit respiratory pathogens, and in some cases ruling out diagnosis of pneumonia by using metagenomic analysis of clinical samples following microbial DNA enrichment. Results discordant with cultures highlight potential technical failures of sequencing, probable missed pathogens by cultures, and conceptual challenges in interpreting the output of sensitive new technologies against an insensitive reference standard. Further study is needed with real-time application of respiratory metagenomics for assessment of impact on antibiotic regimens and clinical outcomes.
67-B  Poster: The Clinical Spectrum of Groove Pancreatitis is Much Wider Than it is Believed

Presenter: Kohtaro Ooka, Clinical Fellow

Research Interest: Clinical Gastroenterology, Hepatology and Nutrition

Mentors: Dhiraj Yadav MD MPH

Authors: Kohtaro Ooka MD, Harkirat Singh MD, Matthew Warndorf MD, Andrew Althouse PhD, Anil Dasyam MD, Georgios Papachristou MD PhD, Adam Slivka MD PhD, Dhiraj Yadav MD MPH

Introduction: Groove pancreatitis (GP) and related entities collectively called “paraduodenal pancreatitis” are an uncommon form of pancreatitis characterized by inflammation in the “groove” between the duodenal wall and pancreatic head. Pathophysiology of GP is unclear but is thought to involve aberrant drainage of the pancreas and/or heterotopic pancreatic tissue in the duodenal wall. Although definitive diagnosis is made on pathology, characteristic radiographic features may allow for a clinical diagnosis of GP. Rates of surgery can be as high as 50% when diagnosis is based on surgical pathology.

Methods: Using natural language processing, we retrospectively identified and reviewed medical records of all patients who received inpatient care at our institution from 2000-2014 and in whom GP was mentioned in their records. CT and MRI for patients with a clinical history consistent with GP was reviewed by an abdominal radiologist. Only patients whose diagnoses of GP were confirmed by imaging were included in the final cohort.

Results: Forty-eight patients (mean age 53.2 years; 79% male; 69% alcohol etiology) met our inclusion criteria. Radiographic findings are shown in Table 1. The most common symptoms were abdominal pain (94%), nausea (71%), vomiting (58%) and weight loss (48%). Serum amylase or lipase elevation above 3x ULN was present in only 33% patients. Prior history of acute (AP), chronic (CP) or any pancreatitis was present in 63%, 44%, and 69% of patients respectively. One-fourth had pre-existing diabetes and 29% had a prior cholecystectomy. During index admission (mean length of stay 4.5 days), no patient had organ failure, 11% had pancreatic necrosis, 17% had gastric outlet obstruction, 19% required enteral feeds or parenteral nutrition and there were no deaths. During follow-up (mean 5 ±2.9 years), 68% of patients had at least one pancreatitis-related readmission, 17% developed new CP and 25% died (4.2% pancreatitis-related). Enteral nutrition, parenteral nutrition or both was required in 17%, 10% and 8% patients. Overall, 29% of patients required enteral or parenteral nutrition during the study period. The incidences of pancreatitis-related readmission, new CP, new diabetes, death from any cause and pancreatitis-related death were 69, 8, 2.9, 5.38 and 0.83 per 100 patient-years respectively. Pancreatitis-related surgery (other than cholecystectomy) during index-admission or follow-up was needed only in 15% patients (Figure 1). The frequency of clinical events did not differ based on prior history of AP or CP.

Conclusion: Clinical recognition of GP impacts management. Most patients with GP can be managed medically and only a minority need surgery. Severity of GP during index admission appears to be milder than traditional AP. However, patients with GP have a high risk of readmissions.
**Poster: Impact Of T-Cell Mediated Allograft Rejection And Antibody Mediated Rejection Within The First Year After Kidney Transplantation**

**Presenter:** Itunu Owoyemi, Clinical Fellow

**Research Interest:** Clinical Renal-Electrolyte

**Mentors:** Sundaram Hariharan MD

**Authors:** Itunu Owoyemi MD, Dana Jorgensen PhD, Srijan Tandukar MD, Sundaram Hariharan MD, Rajil Mehta MD

**Introduction:** This study evaluated the impact of Clinical and Sub-clinical T-Cell-Mediated Rejection (TCMR), Sub-Clinical Inflammation and Antibody Mediated Rejection (ABMR) within the 1st year post-kidney transplantation.

**Methods:** Kidney transplant patients who underwent protocol biopsies at 3 and 12 were included. We sub-classified patients into 5-groups (GR): GR-I: No inflammation (NI) in one or both biopsies, GR-II: Subclinical-Inflammation (SCI), GR-III: SC-TCMR, GR-IV: C-TCMR, GR-V: ABMR in 1 biopsy. Cumulative allograft histology for acute (i+t+v+g) and chronic (ci+ct+cv+cg) inflammation were analyzed. The burden of renal disease was calculated using Area Under the Curve (AUC: serum creatinine mg*month/dL) for each group. In addition, Graft-Loss, Impending Graft-Loss (eGFR<20 mL/min per 1.73 m2) and Patient-Loss were measured.

**Results:** Recipient and donor demographics and variables were similar across groups. Higher rates of graft loss, impending graft loss were noted among patients with ABMR and C-TCMR as opposed to NI, SCI- and SC-TCMR. The cumulative acute and chronic allograft scores were higher among patients with C-TCMR and ABMR in both 3/12-month biopsies.

**Conclusion:** C-ABMR and C-TCMR within the 1st year were associated with worse renal function, progressive renal dysfunction and higher allograft inflammatory and chronic scores.
**Poster: Daylight Saving Time and Nursing Home Falls**

**Presenter:** Pratik Pandit, Clinical Fellow

**Research Interest:** Clinical Geriatric Medicine

**Mentors:** John Naumovski MD

**Authors:** Pratik Pandit MD, Alison O'Donnell DO, Amanda Hurst, John Naumovski MD

**Introduction:** Daylight saving time (DST) is practiced throughout much of the United States and involves advancing the clock forward 1 hour in the spring and back 1 hour in autumn. Numerous studies exist exploring the impact that DST may have on various factors, including vehicle associated injuries, myocardial infarctions, and work related accidents. To our knowledge, the effect of DST on the nursing home population has never been explored. Falls are an important incident measure in nursing homes and are the focus of many studies looking to reduce such events. Based on prior studies looking at the potential complications of DST in the community, we chose to evaluate the impact of DST on fall incidents in the nursing home setting. Given the regimented schedule of the nursing home environment, nursing home residents may have less capacity to adapt to DST transitions. Therefore, we hypothesized that there would be an increased incidence of falls among nursing home residents after DST transition periods.

**Methods:** We reviewed the incident reports from a single nursing home facility in Pittsburgh, Pennsylvania from January 2016 to August 2018. Fall incidents were reviewed for both 1 week prior and 1 week after each DST transition period as well as 3 weeks prior and 3 weeks after. Spring and autumn DST transitions were analyzed both together and separately.

**Results:** There was no statistically significant difference in falls when falls 1 week before a DST transition (n = 25) were compared to falls 1 week after a DST transition (n = 33) (P = 0.36) or when falls 3 weeks before a DST transition (n = 83) were compared to falls 3 weeks after a DST transition (n = 79) (P = 0.81). Additionally, there was no statistically significant difference when events in the spring and autumn were analyzed separately.

**Conclusion:** From our data, there does not appear to be a correlation between DST transitions and fall incidents in the nursing home setting.
**Poster: Mucin 1 Is Necessary for Normal Bone Architecture and TrpV5 Localization in the Kidney's Distal Convoluted Tubule**

**Presenter:** Evan Ray, Junior Faculty

**Research Interest:** Clinical Renal-Electrolyte

**Mentors:** Thomas Kleyman MD

**Funding Source:** K08

**Authors:** Evan Ray MD PhD, Mohammad Al-Bataineh DVM MS PhD, Allison Marciszyn PhD, Paul Poland PhD, Christopher Santucci, Harry Blair MD, Thomas Kleyman MD, Rebecca Hughey MD

**Introduction:** Mucin 1 (Muc1 in mice and MUC1 in humans) is a heavily glycosylated transmembrane protein expressed in numerous epithelia. Muc1 interacts with other glycoproteins via interaction with galectins, which bind beta-galactoside sugars. Genome-wide association data suggest a link between MUC1 polymorphism and bone density. MUC1 exogenously expressed in cultured cells physically interacts with calcium-selective ion channel TRPV5, increasing cell surface expression and activity in a galectin 3-dependent fashion. TRPV5 knock-out (KO) mice exhibit impaired reabsorption of filtered Ca2+ in the kidney's distal convoluted tubule (DCT), as demonstrated by hypercalciuria and diminished trabecular and cortical bone thickness. We hypothesize that interaction between Muc1 and TrpV5 is necessary for normal Ca2+ homeostasis and bone architecture.

**Methods:** We examined density and architecture of bone in Muc1 KO mice compared to controls. We examined blood calcium levels in whole blood via iSTAT. Blood Ca2+ levels are tightly regulated, but Ca2+ depletion results in increased expression of 1-alpha-hydroxylase. We examined 1-alpha-hydroxylase expression via Western blot. Further, we examined localization of TrpV5 in Muc1 KO mice and in Galectin-3 KO mice using immunofluorescence microscopy.

**Results:** Male Muc1 KO mice exhibit reduced lumbar vertebral cortical and trabecular thickness, with increased surface area/volume. Muc1 KO mice exhibit similar whole-blood ionized Ca2+ levels, but increased kidney 1-alpha-hydroxylase levels, suggestive of bodily Ca2+ depletion. Evidence that this may occur secondary to urinary Ca2+ wasting comes from our observation that TrpV5 is mis-localized in the DCT of Muc1 KO mice. Additionally, TrpV5 is mis-localized in the DCT in galectin-3 KO mice, consistent with a role for galectin 3 in mediating Muc1-TrpV5 interaction.

**Conclusion:** Taken together, these findings suggest that Muc1 plays a role in bodily Ca2+ homeostasis and bone physiology.
**72-B Poster: SGLT2 Inhibition in the Management of Intractable Hypomagnesemia**

**Presenter:** Evan Ray, Junior Faculty  
**Research Interest:** Clinical  
Renal-Electrolyte  
**Mentors:** Thomas Kleyman MD  
**Funding Source:** K08  
**Authors:** Evan Ray MD PhD, Cary Boyd Shiwarski MD PhD, Danica Novacic MD, David Cassiman MD PhD

**Introduction:** Hypomagnesemia can be challenging to treat, with conventional therapies often failing to normalize serum magnesium levels or alleviate symptoms. Glucose intolerance frequently accompanies hypomagnesemia. Reasoning that renal tubular reabsorption of magnesium could be enhanced by diverting sodium reabsorption from the proximal tubule to more distal nephron segments, we evaluated the ability of type 2 sodium glucose co-transporter (SGLT2) inhibitors to increase serum magnesium levels in patients with urinary wasting of magnesium and diabetes mellitus.

**Methods:** Three patients were selected with urinary magnesium wasting and intractable hypomagnesemia. Two of these experienced hypomagnesemia as a consequence of HNF1B deletion; the third was idiopathic. Each patient was started on a different SGLT2 inhibitor: canagliflozin, empagliflozin, or dapagliflozin. Serum electrolyte levels were monitored regularly and compared to historical values. Twenty-four hour urine collections were performed and used to assess the changes in fractional excretion of magnesium before and after initiation of the SGLT2 inhibitor.

**Results:** All three patients demonstrated improved serum magnesium levels, with a mean increase of 0.36 ± 0.12 mg/dL (0.15 ± 0.05 mmol/L). In one patient who had been requiring two daily infusions of intravenous magnesium, levels normalized and infusions were held. Serum magnesium levels after SGLT2 inhibitor initiation were higher than they had been in the context of intravenous infusion. All three patients experienced higher average magnesium levels than at any point in their medical history. All three experienced symptomatic improvement. Fractional excretion of magnesium declined in both patients with HNF1B mutations, but did not improve in the third patient.

**Conclusion:** These findings demonstrate that SGLT2 inhibitors can be effective in at least some patients with previously intractable symptomatic hypomagnesemia. Increased renal tubular reabsorption of magnesium may contribute to this phenomenon.
**Poster:** Long Term Mortality and Readmissions After Transcatheter Aortic Valve Replacement

**Presenter:** Mourad Senussi, Clinical Fellow

**Research Interest:** Clinical Cardiology

**Mentors:** Suresh Mulukutla MD

**Authors:** Mourad Senussi MD, John Schindler MD, Ibrahim Sultan MD, Ahmad Masri MD, Forozan Navid MD, Dustin Kliner MD, Arman Kilic MD, Michael Sharbaugh MPH, Amr Barakat MD, Andrew Althouse PhD, Joon Lee MD, Thomas Gleason MD, Suresh Mulukutla MD

**Introduction:** Readmissions following transcatheter aortic valve replacement (TAVR) are common but detailed analysis of cardiac and non-cardiac inpatient readmissions beyond thirty days to different levels of care are limited.

**Methods:** Our study population was 1,037 patients who underwent TAVR between 2011-2017 within a multi-hospital quaternary health system. Readmissions were adjudicated and classified based on primary readmission diagnosis (cardiac versus noncardiac) and level of care (intensive care unit (ICU) admission vs non-ICU admission). Incidence, causes, and outcomes of readmissions to up to three years post procedure were evaluated.

**Results:** Of the 1,017 patients who survived their index hospitalization, there were readmissions due to noncardiac causes in 350 (34.4%) and cardiac causes in 208 (20.5%) during a mean 1.96 years of follow-up. The most common non-cardiac causes of readmission were sepsis/infection (14.3%), gastrointestinal (8.3%), and respiratory (4.8%), whereas heart failure (14.0%) and arrhythmias (4.6%) were the most common cardiac causes of readmission. A total of 191 (18.8%) patients were readmitted to the ICU and 372 patients (36.6%) were non-ICU readmissions. The risk of a noncardiac readmission was highest in the period immediately following TAVR (~ 4.5% per month) with an early high hazard phase that gradually declined over months. However, the risk of cardiac readmission remained stable at ~ 1% per month throughout. TAVR patients that were readmitted for any cause had markedly increased mortality; this was especially true for patients readmitted to an ICU.

**Conclusion:** In TAVR patients who survived their index hospitalization, non-cardiac readmissions were more prevalent than cardiac. The risk of readmission and subsequent mortality was highest immediately post-procedure and declined thereafter. Readmission to ICU portends the highest risk of subsequent death in this cohort.
**Poster: The Utility of PSA surveillance during Testosterone Replacement Therapy (TRT)**

**Presenter:** Shreya Subramaniam, Clinical Fellow

**Research Interest:** Clinical Endocrinology and Metabolism

**Mentors:** Alexandra Clark MD

**Authors:** Shreya Subramaniam MD, Alexandra Clark MD, R Harsha Rao MD

**Introduction:** Testosterone replacement therapy (TRT) can lead to prostatic epithelial cell proliferation resulting in benign prostatic hyperplasia (BPH) and/or the unmasking/progression of prostate cancer. How to monitor prostate health during TRT remains controversial, but Endocrine Society guidelines recommend screening with Prostate Specific Antigen (PSA) and rectal examination after 3 to 12 months, with race- and age-appropriate monitoring thereafter, based on shared decision-making with patients, and a consensus that PSA=4ng/ml merits urological evaluation. Concerns have also been raised that surveillance increases the risk of prostate biopsies for subclinical prostate disease.

**Methods:** We performed detailed chart reviews of 361 male veterans aged >40 years (Mean?SE 62?0.5y) prescribed TRT for =12months (Mean 51?1.3months) to determine whether (a) they developed prostate disorders after starting TRT, defined as one or more of the following: new lower urinary tract symptoms (LUTS), new medications for LUTS, need for urologic consultation, new urinary obstruction, and/or a new diagnosis of BPH, and (b) whether PSA surveillance was instrumental in the detection of prostate cancer.

**Results:** A prostate disorder developed on TRT in 34.9% of patients (126/361), of whom 57(15.8%) experienced new LUTS, 86(23.8%) required medications for new/worsening LUTS, and 65(18.3%) were referred to Urology for either LUTS (25[38.4%]), urinary obstruction (9/65[13.8%]), or PSA>4ng/ml (31[47.7%]). Of those referred for PSA>4ng/ml, 17(54.8%) underwent biopsy, which revealed prostate cancer in 6(19.3%), and high-grade prostate intraepithelial neoplasia (HGPIN) in 3 (9.7%). We also examined whether Initial PSA=4ng/ml was a marker of risk for prostate problems on TRT. Of ten such patients, PSA regressed to <4ng/ml on TRT in 4 patients, whereas it remained =4ng/ml in 6. However, patients with initial PSA>1ng/ml were ten times more likely to develop PSA=4ng/ml (34/153[22.2%]) than with initial PSA=1ng/ml (4/208[1.9%], p=<0.001).

**Conclusion:** The general consensus that TRT does not cause prostate cancer had led to doubts being cast on the utility of using annual PSA surveillance for prostate cancer during TRT. Notwithstanding its rarity—only six of 361 patients on TRT for an average of ~4 years were diagnosed with prostate cancer—our data suggest that such surveillance is warranted. PSA>4ng/ml prompted a biopsy in more than half of the 31 patients referred for urologic consultation, resulting in a diagnosis of either cancer in 6 patients, or precancerous lesions in 3 others, representing a clinically significant yield of 29%.
**Poster:**** Solid organ transplant (SOT) recipients as a model population to study carbapenem resistant Enterobacteriaceae (CRE) infections: How well do new anti-CRE agents perform?**

**Presenter:** Jonathan Sun, Clinical Fellow

**Research Interest:** Clinical Infectious Diseases

**Mentors:** Minh-Hong Nguyen MD

**Authors:** Jonathan Sun DO

**Introduction:** CRE have emerged as major pathogens globally. SOT recipients are a model population to study treatment of antimicrobial-resistant infections, because levels of immunosuppression make good outcomes especially dependent upon drug effectiveness. In March 2015, FDA approved ceftazidime-avibactam (CAZ-AVI), the first new anti-CRE agent to arrive in the clinic. Our objective was to evaluate whether CAZ-AVI fulfills the need to improve outcomes among SOT recipients with CRE infection.

**Methods:** We performed a retrospective study of SOT recipients infected with CRE since 2012, who were treated with CAZ-AVI or salvage agents for = 3 days.

**Results:** Thirty-five CRE-infected SOT recipients were identified (14 liver, 11 lung, 6 kidney, 3 intestine, 1 heart). Types of infections were bacteremia (20), pneumonia (11), intra-abdominal abscess (3) and soft tissue infection/osteomyelitis (1). Sixteen and 19 patients were treated with CAZ-AVI and salvage agents, respectively. Types of infection or SOT, SOFA scores and APACHE II scores did not differ significantly between patients treated with CAZ-AVI or salvage agents. Thirty- and 90-day mortality rates were significantly lower among SOT recipients treated with CAZ-AVI (0% and 6%, respectively) compared to salvage agents (26% and 37%, respectively; p=0.049 and 0.047). Among patients who survived 90 days, recurrent CRE infections were diagnosed in 53% of those treated with CAZ-AVI and 25% treated with a salvage regimen (p=0.24). Median time from end of therapy to recurrent infection was 91 days (range 1 to 799) and 92.5 days (range 1 to 583) with CAZ-AVI and salvage regimens, respectively. CAZ-AVI resistance developed in 37% (n=3) of patients with recurrent infections.

**Conclusion:** Despite a small sample size, our study identifies major limitations with our current management of CRE infections. Although CAZ-AVI significantly reduced short-term mortality among SOT recipients with CRE infections compared to salvage regimens, it did not reduce recurrent CRE infections. Moreover, recurrent CRE infections following CAZ-AVI treatment were often caused by resistant strains. These data suggest that CAZ-AVI does not effectively eliminate CRE within a niche of colonization in the GI tract, which is the likely source of recurrent infections and emergence of resistance. We are currently performing whole genome sequencing and phylogenetic analysis of CRE strains causing GI colonization and infection in SOT recipients. Future studies will need to address the duration of CRE GI colonization, and therapy to eliminate GI colonization.
76-B  **Poster:** Differential Networks of Circulating Inflammatory Mediators in HIV-Infected and Uninfected Individuals

**Presenter:** Lena Vodovotz, Undergraduate Student

**Research Interest:** Clinical Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** R01, K24, UL1

**Authors:** Lena Vodovotz Undergraduate, Ruben Zamora PhD, Shulin Qin MD, Seyed Mehdi Nouraie PhD, Meghan Fitzpatrick MD, Cathy Kessinger RN, Lawrence Kingsley DrPH, Kristina Crothers MD, Laurence Huang MD, Alison Morris MD

**Introduction:** HIV is an independent risk factor for various pulmonary diseases. While systemic inflammation is thought to contribute to worsening lung function in HIV, the effect on inflammatory milieu caused by both smoking and HIV infection has not yet been elucidated. We therefore sought to determine associations between systemic inflammatory networks, HIV status, smoking status, and measures of pulmonary function.

**Methods:** Study participants were HIV-infected and uninfected individuals enrolled in the Pittsburgh HIV Lung Cohort. Demographic and clinical characteristics were collected via chart abstraction or participant self-report. All participants performed pulmonary function tests (PFTs) according to American Thoracic Society guidelines. Plasma levels of Interleukin (IL)-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17a, G-CSF, GM-CSF, TNF-a, IFN-?, CCL2, CCL4, C-Reactive Protein (CRP) and endothelin 1 (ET1) were measured by Luminex or ELISA. Inflammatory mediator networks were generated using MATLAB™. Network connections were generated if the correlation coefficient between 2 inflammatory mediators was = 0.8. Networks were stratified by HIV status, smoking status, and either diffusing capacity for carbon monoxide (DLCO) or forced expiratory volume in 1 second (FEV1) % (< 80 or = 80 percent predicted).

**Results:** 380 HIV+ (256 men, 265 smokers) and 148 HIV- individuals (80 men, 90 smokers) were included in the analysis. Regardless of HIV or smoking status, inflammatory mediator networks of individuals with FEV1 or DLCO % predicted < 80 were more complex than those of participants with FEV1 or DLCO % predicted = 80. The network connectivity of individual inflammatory mediators was assessed and ranked by total number of connections. Based on this analysis, the most connected cytokines across all participant subgroups, regardless of HIV, smoking status, DLCO, or FEV1, were IL-2, IL-17A, and IL-7. Plasma levels of TNF-a and IL-17A were strongly correlated in all HIV+ groups (suggesting presence of effector memory T-cells), but correlations were greatly reduced in HIV- groups.

**Conclusion:** Increased network complexity in groups with DLCO or FEV1 percent predicted < 80 suggests that worse pulmonary function is associated with increased systemic immune activation. The high network connectivity of IL-17A suggests that the Th17 cell lineage may be of importance at the junction of HIV and lung disease. Additionally, the increased correlation between TNF-a and IL-17A only in HIV+ groups suggests an upregulation of effector memory T-cell activity in HIV. Further research will be necessary to determine the specific effects of HIV and smoking on inflammatory milieu as it relates to lung health.
**Poster: Difficulties in Diagnosing and Managing Gram Positive Rod Endocarditis: A Single Center Case Series.**

**Presenter:** Phillip Wagner, Medical Student

**Research Interest:** Clinical Infectious Diseases

**Mentors:** Kathleen Sheridan DO

**Authors:** Phillip Wagner MS, Kathleen Sheridan DO, Mana Rao MD, Marini Rachel MD

**Introduction:** Cases of endocarditis (IE) due to gram positive rods (GPRs) have their own epidemiology and unique presentations, and therefore present challenges in diagnosis and management. We discuss these diagnostic and management difficulties.

**Methods:** We performed a retrospective review of all patients admitted to the University of Pittsburgh Medical Center Presbyterian Campus between 2011 and 2017. Inclusion was based on the Duke Criteria and identification of a GPR as the causative organism.

**Results:** Three of the 11 patients had lab errors resulting in mis-identification of the pathogen. Two patients were misdiagnosed, causing a delay in diagnosis treatment. Average speciation took 5.8 days from presentation; susceptibilities took an average of 9.3 days. Only the patient with Nocardia IE expired while inpatient. None of the other 10 patients were readmitted during the next year for reasons related to IE.

**Conclusion:** Subtleties in clinical presentation, delays in laboratory identification, and the rarity of experience with these pathogens could all complicate management of GPR IE. Physicians should have a high level of suspicion when these organisms are identified and chose empiric regimens accordingly.
**79-B Poster**: A dose-response association between social determinants of health and suicide ideation and attempt

**Presenter**: Camille Davis, Medical Student

**Research Interest**: Epidemiology
- General Internal Medicine Affiliated

**Mentors**: John Blosnich PhD

**Funding Source**: VISN-4 Competitive Pilot Program

**Authors**: Camille Davis BSc, John Blosnich PhD

**Introduction**: Suicide is the 10th leading cause of death in the US, increasing 33% from 1999-2017. Although over 80% of suicide decedents had a medical visit in the year preceding their deaths, healthcare systems struggle to identify risk factors for suicide. Social determinants of health (SDH) are strong predictors of suicide risk, and military Veterans, a population with high risk for suicide, are uniquely exposed to negative SDH such as violence and homelessness. Despite increasing national emphasis for healthcare systems’ electronic health records (EHR) to include SDH data to inform patient treatment and outcomes, most EHR do not include SDH data. The objectives of this project were (1) to determine the extent to which SDH are detectable in the Veterans Health Administration (VHA) EHR and (2) examine the associations between SDH and suicide ideation and attempt (i.e., suicide morbidity).

**Methods**: Data are from patients in the Veterans Integrated Service Network Region 4 with >1 visits during 2016 (n=293,872). SDH were operationalized using VHA coding for receipt of specific services (e.g., housing services) and ICD-10 codes (e.g., adult maltreatment), encompassing 6 categories: violence, housing instability, financial/employment problems, legal problems, familial/social problems, and lack of access to care/transportation. Suicide morbidity was defined by ICD-10 codes. Logistic regression produced the associations of SDH with suicide morbidity, adjusting for sociodemographics and medical comorbidities (i.e., Elixhauser Index).

**Results**: Within this cohort, most patients were white (79.7%), male (91.7%), and = 60 years of age (70.9%). One in ten patients had 1 SDH and 5.6% of patients had at least 2 SDH. Regarding suicide during 2016, 0.9% of patients had suicide ideation while 0.1% of patients made a suicide attempt. After adjusting for sociodemographics and medical comorbidity, there was a dose response-like relation between the number of SDH occurrences and suicide morbidity. For instance, compared to patients with no SDH, the adjusted odds of suicide attempt for patients with 1 SDH was 4.9 (99%CI:3.3-7.2), with 2 SDH was 8.0 (99%CI:5.1-12.6), with 3 SDH was 10.4 (99%CI:6.2-17.6), with 4 SDH was 14.2 (99%CI:7.6-26.5), with 5 SDH was 25.1 (99%CI:12.3-51.1), and all 6 SDH was 44.6 (99%CI:17.6-112.5).

**Conclusion**: SDH were the variables most strongly associated with suicide morbidity. Suicide remains a complex phenomenon that requires broader perspectives on surveillance, prevention, and treatment. Thus, standardized integration of SDH information into health care systems could be a major step toward improving mental health care, suicide prevention, and intervention strategies.
80-B **Poster:** INVESTIGATING THE ASSOCIATION OF NEIGHBORHOOD WALKABILITY WITH RISK FACTORS FOR CARDIOVASCULAR DISEASE AMONG RECENTLY HOSPITALIZED PATIENTS WITH SYSTOLIC HEART FAILURE.

**Presenter:** Zaneta Franklin, Medical Student

**Research Interest:** Epidemiology
General Internal Medicine

**Mentors:** Bruce Rollman MD

**Authors:** Zaneta Franklin BSc, Kwonho Jeong MS, Scott Rothenberger PhD, Julia Holber BA, John Jakicic PhD, Steven Albert PhD, Bruce Rollman MD

**Introduction:** Neighborhood walkability has been associated with the risk of cardiovascular disease (CVD) in healthy community samples; however, few studies involved medically ill populations. We investigated the relationship between neighborhood walkability and several risk factors for CVD and mood symptoms among a cohort of recently hospitalized patients with systolic heart failure (HF) who consented to enroll into a clinical trial.

**Methods:** From March 2014 to Oct 2017, we screened hospitalized patients with systolic HF (ejection fraction (EF) =45%) and NYHA class II-IV symptoms for depression at 8 Pittsburgh-area hospitals. Two weeks after discharge, we telephoned consented patients to confirm protocol-eligibility, administer our baseline assessment battery and conduct a detailed chart review. We obtained the WalkScore™ for each patient’s address that classified their neighborhood’s walkability on a 0-100 scale based on routes to schools, parks, food markets, and other retail (https://www.walkscore.com/professional/research.php), and further categorized these scores into four separate 25-point WalkScore™ categories: Very Car-Dependent, Car-Dependent, Somewhat Walkable, and Very Walkable. We then assessed the relationship between each category and NYHA class, EF, BMI, PHQ-9, medication count, and co-morbidity adjusting for age, gender, race, and marital status.

**Results:** Among our 756 HF patients (mean age: 66±13, 44% female, 74% White, mean BMI 32.6±9.3, median WalkScore 32[8,53]), living in a car-dependent neighborhood was associated with older age (p=0.006), White race (<0.001) and marital status(p<0.001), but not diabetes (mean A1C 8.4±4.6), hypertension, hyperlipidemia, total number of comorbidities, BMI, or mood symptoms (PHQ-9). Unexpectedly, systolic blood pressure was highest in the Very Walkable group (systolic:133±21) vs. Very Car-Dependent (122±19) (p<0.001) even after adjustment for age, race, and marital status.

**Conclusion:** While increased neighborhood walkability has been associated with reduced risk of CVD in relatively healthy populations, this association may be attenuated in HF patients who may be unable to take advantage of neighborhood walkability. Further analyses are needed to better understand why blood pressure control was worse in more walkable areas and the prognostic potential of neighborhood walkability for HF morbidity.
Poster: The combined associations of physical activity and sleep with depressive symptoms in women with young children.

Presenter: Marquis Hawkins, Junior Faculty

Research Interest: Epidemiology
General Internal Medicine Affiliated

Mentors: Esa Davis MD

Funding Source: KL2

Authors: Marquis Hawkins PhD, Daniel Buysse MD, Kaleab Abebe PhD, Judy Chang MD, Kathleen Mctigue MD, Esa Davis MD

Introduction: Women with young children are at increased risk for depression, which can adversely affect the long-term health of both mother and child. Health behaviors including physical activity (PA) and sleep have been identified as independent risk factors for depression. Traditionally, researchers have examined the PA-depression and sleep-depression relationships separately; however, PA and sleep behaviors are linked through the circadian timing system. Considering sleep and physical activity together may provide new insights on how to maximize mental health benefits in women with young children. The aim of this analysis is to examine the combined associations of PA and sleep with depressive symptoms in women with young children.

Methods: We analyzed data from the National Health and Nutrition Examination Survey (2007-2014). We included women with children < 5 years of age, not pregnant, with complete data on physical activity, sleep, and depressive symptoms (n=1,222). The primary exposures were self-reported physical activity (some vs. none) and sleep duration (>6 vs. <6 hours/night). The primary outcome was moderate-to-severe depression (referred to as “depression” going forward). Multivariable logistic regression was used to compare odds of depression by engagement in PA and sleep individually or in combination. No PA and short sleep duration (<6 hours/night) was the reference group.

Results: Participants had a mean age of 31.2 yrs and their youngest child had a mean age of 2.33 yrs. Approximately 48%, 82%, and 40% performed some PA, slept >6 hours/night, and both respectively. Depression was prevalent in 10% of the sample. Engaging in some PA and sleeping >6 hours/night were associated with an unadjusted 0.41 (95% CI 0.26 to 0.64) and 0.40 (95% CI 0.25 to 0.64) odds of depression. The combined associations of engaging in some PA and sleeping >6 hours/night were more strongly associated with depression (OR = 0.16, 95% CI 0.09 to 0.29) than either behavior alone. This relationship persisted after adjustment for education, race/ethnicity, marital status, obesity, poverty status, and the child's age (OR = 0.19, 95% CI 0.10 to 0.38).

Conclusion: PA and sleep, considered separately and in combination, were associated with better mental health in women with young children. The combination of adequate PA and sleep may have greater mental health benefits than either behavior alone. Future studies should examine the effects of promoting PA and sleep on postpartum depression in women.
Introduction: Exposure to pollutants such as fine particulate matter (PM2.5) has been associated with cardiovascular events. Allegheny County has historically had elevated concentrations of PM due to its industrial history and continues to have high concentrations today. PM2.5 and atrial fibrillation (AF) has had limited investigation; we examined the relation of PM2.5 and increased risk of stroke in individuals with prevalent AF.

Methods: We queried the UPMC electronic health record from 2007-2015 to identify residents of Allegheny County with AF. We employed a validated algorithm combining electrocardiography and International Classification of Disease (ICD) coding to identify incident AF, excluding individuals age <18 years, history of stroke or transient ischemic attack prior to AF, or cardiac surgery within 30 days of AF diagnosis. We applied ICD coding to identify relevant covariates (hypertension, diabetes, peripheral arterial disease, coronary artery disease, heart failure) and date of incident stroke. We geocoded individual addresses and estimated PM2.5 exposure based on land use regression models derived from spatial saturation monitoring across the region, temporally calibrated using Environmental Protection Agency regulatory monitoring data. We estimated median household income and education by identifying the Census block groups of participant residence. We determined associations of PM and stroke in our cohort with Cox proportional multivariable-adjusted hazards models.

Results: Our cohort comprised 31,102 individuals (age 74.3±13.6, 50.0% women) with a median follow-up of 3.4 (1.6-5.8) years. The incidence of stroke per 1,000 person-years was 10.6 (95% Confidence Interval [CI]=10.1-11.2). We observed associations between PM2.5 and stroke: after adjusting for age, sex, race and clinical risk factors, we observed a hazard ratio for ischemic stroke (HR) of 1.28 (95% CI=1.09-1.50; P=0.003) among individuals in the highest (vs. lowest) quartile of PM2.5 exposures. Adjusting for median census block group income and education did not attenuate the association between PM and stroke (HR 1.24; 95% CI=1.02-1.51; P=0.03) in individuals with prevalent AF.

Conclusion: We examined a large cohort of individuals with historically elevated exposure to industrial pollution and prevalent AF. Our study demonstrates pollution is an environmental exposure that contributes to stroke risk in AF, even following adjustment for clinical and social factors. Additional study will examine the mechanisms for this association and the contribution of neighborhood-based social determinants with PM and stroke risk in AF.
**83-B Poster:** Healthcare Utilization Patterns and Health Quality Indicators in Sickle Cell Disease Patients Transitioning from Pediatric to Adulthood

**Presenter:** Akshaya Arjunan, Medical Student

**Research Interest:** Health Services Hematology/Oncology

**Mentors:** Laura M. De Castro MD

**Funding Source:** ASH HONORS award

**Authors:** Akshaya Arjunan BS, Sydna Burns, Davlyn K. Nauman, Deborah Moss MD, Laura M. De Castro MD

**Introduction:** With improvements in comprehensive medical care, about 93% of children born with sickle cell disease (SCD) are now living past 18 years of age. However, the majority of SCD-related deaths occur after 18 years and after transfer to an adult provider leaving this young adult population particularly vulnerable with increased health care utilization. This study aims to describe the pattern of HCU and health quality indicators (HQI) in SCD patients at different ages of the transition period.

**Methods:** A retrospective analysis of health insurance claims data for service dates 04/01/2016 through 03/31/2017 was conducted. Members aged 11-35 years old that met the claims-based definition of SCD with 12 continuous months of membership were selected and stratified into three groups representing pre-transition (A: 11-18 yr.), transition (B: 19-26 yr.), and adult (C: 27-35 yr.). Data obtained included demographics, HCU patterns (emergency department (ED) visits, inpatient admissions and diagnosis, 30-day readmission rate, ED reliance ratio (EDR) and total cost of care), and HQI (hydroxyurea (HU) use, HU possession ratio (HPR), influenza vaccination status, and number of PCP and specialist visits).

**Results:** A total of 144 members, 88 (61%) female, fit the inclusion criteria. While the average total cost of care was similar in the three groups, the average cost of ED visits was three times more for Group C compared to A and B. An increase in EDR, acute inpatient admission cost, and readmission rate was noted between Groups A and B. About half (44%) of the patients in Group A had no ED visits during the study period compared to Group B (29%) and Group C (26%). More than 50% of patients in Groups B and C did not have a PCP or specialty visit vs. 25% in Group A. Group B had 13 visits to pediatric Hem/Onc providers, but only one visit to an adult Hem/Onc provider. HPR was roughly 0.25 for each of the groups indicating poor adherence across all ages. Influenza vaccination was less frequent in the transition group, B, than in Groups A and C.

**Conclusion:** Our data shows the vulnerability of SCD patients during their transition years (19-26 yr.) with higher HCU patterns (i.e. EDR, inpatient admissions cost and readmission rate) and lower HQI (i.e. lack of PCP and Hem/Onc visits, lower influenza vaccinations, and HPR). Thus, this study highlights the urgent need for improved protocols and systems in order to provide continuity and quality care during these critical transition years.
Introduction: Studies in adult and pediatric Sickle Cell Disease (SCD) populations have shown that hydroxyurea (HU) reduces the frequency and intensity of SCD painful events and decreases morbidity. Follow-up studies of Multicenter Study of Hydroxyurea (MSH) patients have also shown cost-effectiveness and improved survival for HU users. The overarching aim of this study was to describe the pattern of healthcare utilization (HCU) and health quality indicators (HQI) in a SCD population at different ages of the transition period-data submitted in another abstract. Here we present data supporting patterns of HU utilization and cost in three different SCD patient age-groups.

Methods: A retrospective analysis of health insurance claims data for service dates 04/01/2016 through 03/31/2017 was conducted. Members aged 11-35 years old that met the claims-based definition of SCD with 12 continuous months of membership were selected and stratified into three groups representing pre-transition (A: 11-18 yr.), transition (B: 19-26 yr.), and adult (C: 27-35 yr.). Data obtained included demographics, HCU patterns (emergency department (ED) visits, inpatient admissions and diagnosis, 30-day readmission rate), ED reliance ratio (EDR) and total cost of care), and HQI (hydroxyurea (HU) use, HU possession ratio (HPR), influenza vaccination status, and number of PCP and specialist visits).

Results: A total of 144 members, 88 (61%) female, fit the inclusion criteria. Less than 40% of patients in all three groups had filled HU prescriptions. HU possession ratio was similarly low for all three groups (~0.27) with 1.0 indicating perfect adherence. Those on HU, independent of age groups, had a lower rate of both low and high EDR than those not on HU. For those on HU, Group C was the only one with an increase in high EDR compared with those with low EDR. More non-HU users had not seen a PCP or Specialty within the past year. Average total cost of care for the pre-transition group was similar (~$22,000) between those prescribed HU and those not on HU. Average total cost of care was more than twice as much for Groups B and C on HU vs not on HU.

Conclusion: Despite 20 years of FDA approval for HU as SCD therapy, analysis of insurance data in SCD patients still reveals poor adherence, higher overall total care cost, but lower EDR. This Conundrum supports the needs further emphasis on increasing education towards adherence to HU therapy while continuing to develop new therapeutic interventions towards disease modification and cure.
85-B Poster: Colonoscopy Volume of Colonic Irrigation (VOCI) and Rate of Adequate Bowel Prep and Adenomas per Colonoscopy

Presenter: Jeffrey Dueker, Clinical Fellow

Research Interest: Health Services
Gastroenterology, Hepatology and Nutrition

Mentors: Asif Khalid MD

Authors: Jeffrey Dueker MD, Elyse Johnston MD, John Hileman RN, Asif Khalid MD

Introduction: Colonoscopies with inadequate bowel prep (BP) decrease the detection of adenomas and lead to repeat early follow up exams. There is limited data on the endoscopists’ effort to achieve an adequate exam through water lavage.

Methods: This is a single center prospective study of 7 endoscopists performing colonoscopy from 07/2017-ongoing. Pre-study: 1) All endoscopists took the Boston Bowel Prep Scale (BBPS) on-line educational program (BUSOM/CORI) and a test, 2) a chart with BP images and the respective BBPS scores was placed above the report generator in each endoscopy suite, 3) the BBPS was made the only option to document BP in the colonoscopy template, 4) all patients scheduled for colonoscopy received a standardized Golytely split-prep, 5) current guidelines for follow-up colonoscopy were placed above the report generator in each endoscopy suite. The volume of water instilled into and suctioned out of the colon (Volume Of Colonic Irrigation; VOCI) was documented in the exam report. We report an interim analysis of the association of VOCI with rate of adequate BP (BBPS>1 in each segment) and APC.

Comparisons between means were made with independent samples T-tests (two sample) or ANOVA (multiple samples). Comparisons between medians were made with Mann-Whitney U tests (two sample) and independent samples median tests (multiple samples). Comparisons between categorical variables were made using Chi square tests.

Results: 749 colonoscopies were performed between 7/5/17-1/28/18 (table 1). The VOCI, adequate BP rate and APC all were significantly different between the endoscopists (p<0.001) (table 2). Endoscopists with higher adequate BP rate (>80%) had a significantly higher mean VOCI than endoscopists with a lower adequate BP rate (1246mL vs. 1070mL, respectively, p=0.01). Using a median APC rate of =1.5 as a cut-off, the 4 endoscopists in the higher APC group had significantly higher mean VOCI than the lower APC group (1370mL vs. 1059mL, respectively, p<0.001).

Conclusion: In this interim analysis a higher VOCI correlates with achieving a higher rate of adequate BP (>80%) and a higher APC rate (=1.5). While the variability between the endoscopists suggests multiple factors that impact the subjective assigning of the BBPS and the APC, VOCI may be one indicator of the endoscopists’ effort in achieving a high-quality colonoscopy. These results need to be validated in larger studies.
**Poster Abstracts**

**86-B Poster:** Performance of the Veteran’s Choice Program in Veterans Referred for Colonoscopy

**Presenter:** Jeffrey Dueker, Clinical Fellow

**Research Interest:** Health Services  
Gastroenterology, Hepatology and Nutrition

**Mentors:** Asif Khalid MD

**Authors:** Jeffrey Dueker MD, Asif Khalid MD

**Introduction:** The Veteran’s Choice Program (VCP) allows for veteran referral into the community if care requested cannot be provided by the VA within 30 days. The performance of the VCP for veterans referred for colonoscopy has not been studied in detail.

**Methods:** We evaluated the performance of the VCP for timeliness, quality metrics and utilization among veterans referred for a colonoscopy through the program. We reviewed records of veterans at VA Pittsburgh Health Care System (VAPHS) who underwent colonoscopy through the VCP from 06/2015-03/2017, with at least 6 months of lead time to permit transfer of records. We compared the number of days from VCP referral to scheduled procedure at VAPHS and actual procedure through VCP. Additionally, we examined VCP utilization in a representative sample (5% margin of error, 95% confidence level) of all colonoscopy referrals through VCP.

**Results:** Of 190 colonoscopies performed outside of the VA through VCP, records were absent for 29 exams (15.2%). For procedures with samples taken, pathology results were absent in 14 of 118 (11.9%). Clear post procedure follow up recommendations were absent in 29 of 161 (18%) cases. Colonoscopy quality metrics were deficient in 27-70% of reports. The median difference in number of days from scheduled procedure at VAPHS to actual procedure through VCP was 2 days earlier (p=0.62). VCP utilization was then examined in 350 of 3,855 veterans. Only 26 (7.4%) of veterans referred for colonoscopy had a documented procedure through the VCP, and 231 (66%) had procedures through VAPHS. The median actual wait time for colonoscopy was 61 days for VAPHS procedures and 66 days for VCP procedures, and were not statically different (p=0.15).

**Conclusion:** While the primary objective of the VCP is to decrease veterans wait times for care, our data do not show any improvement in timeliness for colonoscopy. Fragmentation of care occurred in almost one of 5 veterans utilizing VCP for colonoscopy with missing reports and follow-up recommendations. Colonoscopy quality metrics were deficient in large numbers of procedures performed outside of the VA. Finally, the overall utilization of VCP for colonoscopy in eligible veterans was low. Based on these results, we recommend 1) monitoring of timeliness of care outside the VA, 2) requiring timely and complete communication of records to the VA, and 3) requiring and monitoring of quality metrics, be integral components of the VA MISSION Act, which is soon to replace the VCP.
**Poster: Reduction of Opioid Use and Depression within an IBD Medical Home Care Model**

**Presenter:** Jeffrey Dueker, Clinical Fellow

**Research Interest:** Health Services  
Gastroenterology, Hepatology and Nutrition

**Mentors:** Eva Szigethy MD

**Authors:** Jeffrey Dueker MD, Emily Weaver LCSW, Eva Szigethy MD, Jane Kogan PhD, Marc Schwartz MD, William Shrank MD, Siobhan Proksell MD, Trent Emerick MD, Meredith Wallace PhD, Amanda Malecky RN, Oscar Marroquin MD, Yael Goldblum BS

**Introduction:** Chronic opioid use is associated with increased morbidity, mortality, and health care costs in patients with inflammatory bowel disease (IBD). Despite the magnitude of the opioid problem, alternative treatment options have remained limited. Study aims are to: 1) Characterize adults with IBD enrolled in the IBD medical home (MH), an integrated medical-behavioral care model, and were on chronic opioids at baseline; and 2) Compare opioid use and clinical outcomes from baseline to 12 months in the entire sample, and to the subset with persistent opioid use at 12 months.

**Methods:** Patients who were prescribed opioids for at least 2 months at the time of enrollment into the IBD MH from 2015-2018, as determined by clinical data from electronic health records and Pennsylvania PDMP System, were included. Demographic and clinical information was obtained from the IRB-approved IBD MH research registry. Within IBD MH, patients received opioid treatment agreements and comprehensive behavioral care. Patient-reported depression (PHQ9), quality of life (QoL; SIBDQ), and IBD severity (HBI/UCAI) were recorded at baseline and 12 months. Descriptive statistics, paired t-test, and chi-square were completed using SPSS (v24).

**Results:** Of a total 712 total patients in the IBD MH, 153 were using opioids at baseline; 104 met criteria for inclusion. Of the 104, mean age was 36.6 (SD 9.4) with 62% female, 92% white, 73% with CD, 63% with IBD surgery, 27% with FGID, and 73% on non-opioid psychotropic medications at baseline. Over 12 months within IBD MH, 47% of patients engaged with behavioral therapist, 34% with psychiatrist, and 26% with pain anesthesiologist. Of the 72 patients who discontinued opioids, 64% utilized integrated behavioral services while 36% only used IBD medical care. At 12 months, 30.8% (32) of patients continued opioid use. There was a significant reduction in opioid users (by 69.2%). There was improvement in depressive severity ($p=0.002$) and QOL ($p=0.016$) but not IBD severity over 12 months. There was no such significant clinical improvement in patients with continued opioid use at 12 months who were more likely to be female, of minority race, and have higher rates of depression, FGID, and benzodiazepine use and lower QOL compared to those who discontinued opioid use.

**Conclusion:** Participation in an integrated team-based IBD MH was associated with reduction in opioid use and improvement in QOL and depression over a 12-month period. Future studies will focus on better predicting and targeting chronic opioid users who are at risk for poor clinical outcomes.
Introduction: New recommendations call for earlier, more frequent, and more personalized postpartum care. This study examines providers’ views on postpartum care in the light of new recommendations.

Methods: We surveyed 600 randomly sampled U.S.-based pregnancy healthcare providers. Questions about postpartum care related to optimal timing, reasons for its provision, the priority of specific aspects of care and the frequency with which they are provided, as well as barriers to postpartum care and potential solutions, particularly telemedicine. Questions were binary choice, multiple choice, Likert-scale rating, and open-ended. Results were summarized using descriptive analysis, odds ratios, and means-testing. Aspects of care that were performed more frequently than they were valued (or vice versa) were categorized as “inefficiencies.”

Results: Overall survey response rate was 42.7%, with a final sample consisting of 26.3% Obstetrician-Gynecologists (n=62), 26.7% Family Medicine physicians (n =63), and 44.9% Certified Midwives (n=106). Certain types of postpartum care, such as depression screening, were highly valued and routinely performed. Other aspects of care, such as a pelvic exam and counseling about resuming sexual activity, were identified as inefficiencies. Screening for intimate partner violence and opioid and other substance use were performed less often than other forms of similarly-valued care. A minority of providers (25%) regarded telemedicine as a feasible alternative in-person postpartum care, but 44.1% face challenges to implementation.

Conclusion: Priorities and practice for postpartum care were not perfectly aligned and reported average time available with patients suggests certain aspects of care may be traded-off to accommodate others, illustrating critical opportunity costs in postpartum care delivery. Clear guidelines on the highest value care for each visit, and which practitioner should provide that care, could diminish the burden faced by postpartum care providers. Targeted telemedicine for assessment and counseling, combined with in-person visits for physical exam, when needed, might represent a novel approach to comprehensively and efficiently delivering postpartum care.
**Poster: Bringing Home Primary Care to Everyone: A Nurse Practitioner Consult Model**

**Presenter:** Anita Leon-Jhong, Junior Faculty

**Research Interest:** Health Services  
General Internal Medicine

**Mentors:** Susan Saxon CRNP

**Authors:** Anita Leon-Jhong MD, Susan Saxon CRNP, Cindy Wilson

**Introduction:** Many PCPs do not have the time, training or inclination to provide home visits, even as their patients may have difficulty travelling to the office. The goal of the UPMC Home Primary Care program is to fill this gap by providing a consult-style service in collaboration with PCPs. This group includes six nurse practitioners (NP) who cover distinct geographic regions of Pittsburgh. When a UPMC PCP identifies a patient who could benefit from a home visit, a referral order is placed and the patient is scheduled with a nurse practitioner within 1-4 weeks. Common referrals include need for face-to-face (F2F) visit to obtain durable medical equipment (DME) or home health services, management of chronic medical conditions, and evaluation of home safety and support systems. The nurse practitioners have expertise in home-based care, palliative care and community services. The nurse practitioner documents all findings, including physical exam, medication reconciliation and any recommendations, in the electronic medical record. The PCP then decides how to implement changes based on the NP recommendations. Visits are billed through the patient’s insurance and patients pay the same co-pay as for a primary care office visit.

**Methods:** The following information was collected via chart review for all visits. 1. Patient age, sex2. Date of last PCP visit3. Hospitalization in last 6 months4. F2F documented for DME/home health5. Medication issue identified (patient not taking medication properly, adverse effect)6. Goals of care discussed, hospice referral.

**Results:** In 2018, 237 home visits were conducted on 157 unique patients. The patients were predominantly female (61%) with median age of 79 years. 41% of patients had been hospitalized in the 6 months prior to the visit. 13 patients were deceased within 1 year of the visit. The median time since last PCP encounter was 140 days, with 17% of visits occurring on patients who had not seen their PCP in > 1 year. 29% of visits included F2F documentation for DME/home health. In 24% of visits a significant medication issue was identified. Advanced care planning was documented in 8% of visits and 8 patients were referred to hospice.

**Conclusion:** The home primary care consult is a novel model for expanding care to frail and homebound individuals while allowing them to remain under the care of their long-term PCP. More research is needed to see how this model can be most effective; promoting advanced care planning in this vulnerable patient population appears promising.
**Poster Abstracts**

**90-B Poster: Intimate Partner Violence in Middle-Aged and Older Women: Prevalence and Associated Health Conditions**

**Presenter:** Lena Makaroun, Post-Doctoral Fellow

**Research Interest:** Health Services  
Geriatric Medicine

**Mentors:** Melissa Dichter PhD

**Funding Source:** Veterans Health Administration

**Authors:** Lena Makaroun MD, Emily Brignone PhD, Ann-Marie Rosland MD, Melissa Dichter PhD

**Introduction:** Intimate partner violence (IPV) is prevalent in the U.S. and studies in younger women have shown it to be associated with a range of negative health outcomes, including depression, post-traumatic stress disorder (PTSD) and injuries. Recent United States Preventive Services Task Force recommendations indicate evidence to support routine IPV screening for women of childbearing age (age <45) but insufficient evidence for screening older women. In 2014, the VA implemented annual past-year IPV screening for women of all ages seeking primary care services at select sites. The objective of this study was to determine the prevalence of screening positive for IPV in the past-year (IPV+) among women age =45 years and the association of IPV+ with health-related conditions in these women.

**Methods:** Retrospective cohort study of 4,481 female VA patients age =45 years screened for past-year IPV with the Extended Hurt Insult Threaten Scream tool at 13 VA medical centers between 2014 - 2016. Prevalence of IPV+ was calculated for women ages 45-59 years (“middle-aged”) and =60 years (“older”). The association between IPV+ and mental and physical health-related conditions (detected via clinical encounter diagnosis codes) in the 18 months following screening was evaluated in multivariable logistic regression models adjusting for race/ethnicity.

**Results:** Of 4,481 women screened, 2,937 were middle-aged (mean age 51.7) and 1,544 were older (mean age 66.6). Prevalence of IPV+ was 8.7% in middle-aged and 5.1% in older women. In adjusted models among older women, IPV+ was associated with subsequent diagnoses of anxiety (aOR 1.9, 95% CI: 1.1 - 3.3), depression (aOR 3.4, 95% CI: 2.2 - 5.5), PTSD (aOR 2.35, 95% CI: 1.4 - 4.1), headaches (aOR 2.3, 95% CI 1.3 - 4.2), and injuries/burns (aOR 2.2, 95% CI: 1.1 - 4.4). Similar associations were seen for the middle-aged group.

**Conclusion:** This study, which is the largest to evaluate screening for IPV in women over childbearing age, found that IPV remains both prevalent and morbid for middle-aged and older women, suggesting the need to expand routine IPV screening beyond the childbearing years. Screening for IPV in women over age 44 may improve detection and provision of evidence-based services to this vulnerable population.
91-B  Poster: Measuring preconception wellness within the Veterans Health Administration (VHA)

Presenter: Deirdre Quinn, Post-Doctoral Fellow

Research Interest: Health Services
General Internal Medicine

Mentors: Sonya Borrero MD

Funding Source: VA Office of Women's Health Services

Authors: Deirdre A. Quinn PhD, Maria K. Mor PhD, Florentina E. Sileanu MS, Xinhua Zhao PhD, Lisa S. Callegari MD, Laurie Zephyrin MD, Sonya Borrero MD

Introduction: More women in the U.S. are dying in or around childbirth now than 25 years ago. Despite increased attention to preconception care, lack of consensus about implementing or assessing the success of preconception care has stymied progress. In 2016, the Clinical Workgroup of the National Preconception Health and Health Care Initiative proposed nine wellness measures to assess preconception care quality in healthcare systems. As the largest integrated healthcare system in the U.S., VHA is uniquely positioned to lead the way in implementing and evaluating efforts, including preconception care, to improve birth outcomes. This study is the first comprehensive assessment of VHA's performance on measures of preconception wellness.

Methods: We examined national administrative data, including inpatient, outpatient, and fee-basis visits, lab and pharmacy data, and health factors screening data for women Veterans ages 18-45 with at least one pregnancy outcome (ectopic pregnancy, spontaneous abortion, stillbirth, and/or live birth) during FY 2010-2015. After identifying outcomes, we estimated last menstrual period (LMP) from gestational age at the time of the outcome and used LMP as a reference point to assess eight of the nine preconception indicators at various timepoints (e.g., 3 or 12 months prior to LMP); one indicator, pregnancy intention, was not captured in VA administrative data.

Results: We identified 26,556 pregnancy outcomes from 21,234 women Veterans. Just over half (56.6%) were in non-Hispanic white women, 23.4% in non-Hispanic black women, and 10.9% in Hispanic women; the mean age at LMP was 29.8. The majority (77.1%) of pregnancies ended in live birth; 22.4% resulted in spontaneous abortion or ectopic pregnancy, and 0.5% in stillbirth. Nearly one quarter (23.7%) of pregnancies had no evidence of prenatal care; 44.4% of pregnancies had no documented tobacco screening and 49% had no documented depression screening within 1 year prior to LMP; 29.5% of pregnancies occurred to obese women; and only 40.2% of pregnancies in women with pregestational diabetes had a documented optimal HbA1c measurement (<6.5) in the year prior to LMP. Evidence of any STI screening in the year prior to 3 months post LMP was low, as was documentation of prenatal folic acid use; 95% of pregnancies appeared free from exposure in the year prior to LMP to medications under the Workgroup's six classes of teratogenic medications.

Conclusion: Despite the limitations of existing administrative data, monitoring standard measures of preconception wellness can provide benchmarks for improving women's health across systems and communities. Areas for intervention to improve women Veterans' preconception wellness were identified, including weight reduction, optimizing control of diabetes prior to pregnancy, and improved use and documentation of routine health screenings.
**Poster: Low-Value Care for 4 Common Conditions within the Veterans Health Administration**

**Presenter:** Thomas Radomski, Junior Faculty

**Research Interest:** Health Services
General Internal Medicine

**Mentors:** Walid Gellad MD MPH

**Funding Source:** KL2

**Authors:** Thomas Radomski MD MS, Yan Huang MSc, Seo Young Park PhD, Carolyn Thorpe PhD MPH, Joshua Thorpe PhD MPH, Michael Fine MD MSc, Walid Gellad MD MPH

**Introduction:** Low-value care is a major driver of wasteful healthcare spending and exerts physical and psychological harm upon patients. Whereas low-value care affects up to 43% of Medicare beneficiaries, less is known about its prevalence within VA. Our objective was to quantify the frequency and facility-level variation in the use of low-value testing for Veterans managed within the Veterans Health Administration (VA).

**Methods:** Among a national random sample of Veterans enrolled in VA in 2015 (n=1,022,987) we applied a claims-based metric to identify low-value diagnostic testing for 4 uncomplicated conditions: 1) low-back pain, 2) acute sinusitis, 3) headache, and 4) syncope. Examples of such low-value care include low-back imaging within 6 weeks of an initial back pain diagnosis without red-flag symptoms and maxillofacial CT imaging for uncomplicated sinusitis. For headache, we separately assessed low-value head imaging and electroencephalography (EEG). For syncope, we separately assessed low-value head imaging and carotid ultrasonography. For each condition, we determined the overall percentage of Veterans who received low-value care and the range of low-value care across 127 VA Medical Centers (VAMCs), adjusting for sociodemographic and VAMC characteristics. We used Pearson’s correlation coefficient to determine the correlation between Veterans’ use of different types of low-value care for the same condition within VAMCs, focusing on uncomplicated headache and syncope.

**Results:** Of the 343,024 Veterans who had low-back pain, 19,736 (5.8%) received low-value care (VAMC range 3.6-7.7%). Of the 52,889 Veterans who had acute sinusitis, 1,305 (2.5%) received low-value care (VAMC range 1.3-5.1%). Of the 79,176 Veterans with uncomplicated headache, 6,904 (8.7%) received low-value care (head imaging 6,786 (8.6%) and EEG 167 (0.2%)), with an overall VAMC range of 6.2-14.6%. Lastly, 23,776 Veterans experienced uncomplicated syncope, of whom 3,300 (13.9%) received low-value care (head imaging 2,393 (10.1%) and carotid ultrasound 1,390 (5.9%)), with an overall VAMC range of 11.3-16.8%. Undergoing different forms of low-value care for the same condition was significantly correlated for uncomplicated syncope (Rho 0.21, p<0.019) but not headache (Rho 0.13, p=0.157).

**Conclusion:** In a national random sample of Veterans, we identified 2 to 5-fold variation in the use of low-value diagnostic testing for 4 common conditions across VAMCs and that Veterans’ receipt of low-value diagnostic testing for syncope was correlated within VAMCs. These findings highlight the importance of further characterizing the degree to which Veteran and facility-level factors drive these variations as a first step in developing facility-specific policies to mitigate the provision of low-value care.
94-B  **Poster:** Patients’ Priorities for Post-ICU Care

**Presenter:** Leslie Scheunemann, Junior Faculty

**Research Interest:** Health Services
Geriatric Medicine

**Mentors:** Natalie Leland PhD

**Funding Source:** P30 AG024827

**Authors:** Leslie Scheunemann MD, Jennifer White CScd, MOT, OTR/L, Suman Prinjha PhD, Megan Hamm PhD, Timothy Girard MD, Elizabeth Skidmore PhD, Charles Reynolds MD, Natalie Leland PhD

**Introduction:** While intensive care unit (ICU) survival among older adults is improving, poor post-ICU care quality persists. Understanding patients’ needs and priorities is fundamental to improving care quality. This study aimed to describe patients’ priorities, barriers, and facilitators for recovery across the spectrum of post-ICU care.

**Methods:** We conducted a secondary analysis of 40 semi-structured interviews with a maximum diversity sample of ICU survivors conducted at Oxford University from 2006-2008. We used the method of qualitative description to characterize patients’ priorities, barriers, and facilitators for recovery in three post-ICU periods: transition to wards, early period (=2 months) after discharge home, and late period (>2 months) after discharge home.

**Results:** During the transition to the wards, patients' priorities included feeling safe, engaging in basic mobility, participating in self-care, asserting personhood, reconnecting with people, and going home. Early after discharge home, they emphasized enhancing mobility and self-care, reconnecting with people, beginning psychological healing, and resuming previous roles and routines. Priorities during the late period reflected extended time at home. They included engaging in advanced self-care, achieving psychological health, resuming previous roles and routines, and seeking new life experiences. Barriers included ongoing medical issues (e.g., mood disorders, pain, hallucinations, weakness, poor endurance and poor concentration), poor social support (e.g., inadequate communication, incompatible family coping), and health system issues (e.g., lack of support/equipment, problematic staff attitudes, unsupportive policies). Facilitators were often positive analogs of barriers (e.g. staying positive and motivated, seeing progress in recovery, receiving support of family and friends, receiving timely communication, accessing needed equipment, and receiving healthcare provider support). Which barriers and facilitators were most prominent varied across the care continuum.

**Conclusion:** Patients’ priorities for post-ICU care are critical for developing stakeholder-driven clinical guidelines. Next steps should extend these findings among other stakeholders (e.g., family members, healthcare providers, institutionalized and frail older adults) and determine what clinical assessments best identify patient and family needs across the care continuum.
Poster: The Patient-Centered Medical Home in Government-Based and Integrated Delivery and Finance Systems: A Systematic Review

Presenter: Clark Veet, Post-Doctoral Scholar

Research Interest: Health Services
General Internal Medicine

Mentors: Thomas Radomski MD

Funding Source: TL-1

Authors: Clark Veet MD, Thomas Radomski MD, Elizabeth Swart, Charles Wessel, Christopher D'Avella MD, Inmaculada Hernandez PhD, William Shrank MD, Natasha Parekh MD

Introduction: As healthcare payment moves from volume to value-focused, new delivery models aim to coordinate care and improve quality. The patient-centered medical home (PCMH) aims to improve outcomes and decrease costs. Prior studies have shown mixed outcomes regarding the ability of PCMHs to achieve these objectives. Additionally, it is unclear whether PCMHs operating within government-based systems or integrated delivery and finance systems (IDFS) where payers and providers are vertically integrated impact utilization and cost outcomes.

Methods: We performed a systematic review of clinical trials and observational studies that identified PMCH or equivalent interventions. Primary outcomes included emergency department (ED) visits, hospital admissions, outpatient visits, and total cost of care. We categorized PCMHs as operating within government systems (including Veterans Affairs and Indian Health Service), IDFS, and non-IDFS.

Results: A systematic search of PubMed, the Cochrane Library, and Embase from 2004 to April 2017 yielded 13,939 unique publications. 64 studies were included. 29% were government systems, 24% were IDFS, and 47% were non-IDFS. 35 studies reported ED visits with 17 (48%) showing lower ED use. ED visits decreased in 41% of 11 government studies, 75% of 8 IDFS studies, and 38% of 16 non-IDFS studies. 31 studies reported admissions with 11 (35%) showing decreased admissions. Admissions decreased in 50% of 12 government studies, 28% of 7 IDFS studies, and 25% of 12 non-IDFS studies. PCP visits decreased in 8 (47%) of 17 studies. PCP visits increased in all 6 government studies while specialty visits decreased in 50% of 4 government studies. Among IDFS studies, PCP visits decreased in all 4 studies while specialty visits decreased in 1 (33%) of 3 studies. Among 7 non-IDFS studies, PCP visits increased in 42% of studies while only 14% showed decreased specialty care. Total cost of care was reported in 25 (39%) studies. Reduced costs were observed in 60% of 5 government studies, 50% of 8 IDFS studies, and 33% of 12 non-IDFS studies.

Conclusion: Our study uniquely assessed whether PCMH model effectiveness differed between government systems, IDFS, and non-IDFS. ED visits decreased most within IDFS, while hospital admissions decreased most within government systems. Notably, government systems observed an increase in PCP visits. It is unclear if this change reflects the effectiveness of the PCMH model or patient characteristics. Cost reductions were reported in less than half of studies. This study has important implications for understanding how system-based factors affect the success of PCMH interventions.
**Poster: Balancing Confidence and Competence: The Dunning-Kruger Effect Among Critical Care Fellows Enrolled in a Mechanical Ventilation Course**

**Presenter:** Megan Acho, Clinical Fellow

**Research Interest:** Medical Education
- Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Burton Lee MD

**Authors:** Megan Acho MD, Nitin Seam MD, Burton Lee MD

**Introduction:** In 1999, psychologists Justin Kruger and David Dunning described a disconnect between confidence and competence now known as the Dunning-Kruger Effect. They outlined the "above-average effect" in which individuals with low competence overestimate their knowledge and develop inflated self-confidence. Once these individuals receive training, they become more aware of their limitations. This study explores the role of the Dunning-Kruger Effect among fellows enrolled in a mechanical ventilation course.

**Methods:** First-year critical care and pulmonary/critical care fellows from several academic medical centers were enrolled in an intensive mechanical ventilation course between 2017 and 2018. Pre- and post-course data was obtained, including demographics and self-reported confidence levels from 1 to 5, with 1 denoting "complete novice" and 5 "expert." Subjects completed a ventilator waveform examination prior to and following the course, scored out of 100 points. Confidence scores were converted to a "low" (raw score of 1), "medium" (raw score of 2), and "high" (raw score of 3/4/5) scale. Test scores were converted to a 1-5 scale using the equation "competence = [test score/25] + 1." A Confidence-Competence Ratio (CCR) was generated using the equation “CCR = confidence/competence,” with scores = 1 suggesting the learner is well-calibrated, < 1 suggesting under-confidence, and > 1 suggesting over-confidence.

**Results:** 61 and 60 fellows were included in pre- and post-test analyses, respectively. Test scores improved significantly between pre- and post-tests (17.8+/−12.8 versus 47.7+/−22.8, p<0.0001). Within the pre-test group, confidence was unrelated to test performance as there was no significant difference in test scores among those who reported their confidence as "low," "medium," or "high" (14.6+/−9.7, 16.8+/−12.7, 22.1+/−14.7; p=0.09). Within the post-test group, there was a significant difference in test scores among those with varying levels of confidence (29.8+/−20.8, 47.3+/−22.7, 52.0+/−22.4; p=0.03). CCRs also decreased significantly between the pre- and post-tests (1.3+/−0.6, 0.9+/−0.4; p<0.0001). 68% of fellows were relatively overconfident prior to the course (with CCRs >1), while 76% were under-confident post-course (with CCRs <1).

**Conclusion:** Novice learners may have difficulty gauging their own competence, resulting in overconfidence. Our findings illustrate a disconnect between confidence and competence among first-year fellows participating in a mechanical ventilation course, as predicted by the Dunning-Kruger Effect. We also demonstrate that learners became better calibrated (and relatively under-confident) regarding their skill level after completing the course, as measured by our novel Confidence-Competence Ratio. This may have implications on prioritizing pre-clinical training for critical care fellows.
**Introduction:** The US is becoming increasingly diverse from a racial and ethnic perspective; however, the physician workforce has continued to have disproportionately low numbers of medical school graduates from racial and ethnic groups that are described as underrepresented in medicine (URiM). Mentorship has been proposed as one way to increase the recruitment, retention and experience of URiM physicians and trainees. Our objective was to identify and describe mentoring programs for URiM physicians in academic medicine and to identify barriers and facilitators to success of such programs.

**Methods:** We searched PubMed, PsycINFO, ERIC, and Cochrane databases following PRISMA guidelines in June 2017. We included original publications that described a mentoring program, exclusive of mentoring for a procedural skill, which included academic physicians or trainees from URiM backgrounds, and were conducted in the US. Two reviewers independently evaluated all records for eligibility, and abstracted data from included studies.

**Results:** Our search returned 3308 results, of which 2632 references were excluded based on title and abstract. We performed a full text review on 669 manuscripts and 32 articles met our inclusion criteria. Of those, 13 programs were specifically created for URiM participants. Nine of the programs were developed for junior faculty, seven for medical students; two for residents and none for senior faculty. Frequently cited objectives of these programs were to improve research, diversify representation in specific specialty areas and recruit and retain URiM participants. The dyad model of mentoring was the most common, however, several novel models were described which emphasized mentorship across different training levels. Program evaluations were primarily survey-based with high satisfaction scores, although some articles reported objective outcomes including publications, retention, and promotion. Of those that reported objective outcomes, 20 of 20 showed improvement after the development of the mentorship program.

**Conclusion:** This review describes a range of successful mentoring programs for URiM physicians. The traditional dyad model of mentorship remains common, though novel approaches aimed at improving the pipeline are emerging. Overall, the mentorship programs are met with high satisfaction regardless of mentor demographics, and can promote improvement in academic productivity, and recruitment and retention. Our review describes many mentoring programs for URiM physicians, most of which can be readily adapted by institutions depending on their local resources and goals to help promote and URiM physicians in academic medicine.
98-B  Poster: A Text Message Prompt to Improve Feedback Delivery from Faculty to Housestaff

Presenter: Jared Chiarchiaro, Junior Faculty

Research Interest: Medical Education
Pulmonary, Allergy and Critical Care Medicine

Authors: Jared Chiarchiaro MD, Erin Nuzzo MD, Eric Nolley MD, Brian McVerry MD, Robert Arnold MD

Introduction: Learners in medicine often report not receiving feedback or being dissatisfied with the feedback they do receive. Faculty struggle with how to deliver feedback effectively and efficiently. We examined the effect of a text message prompt and didactic on the frequency of feedback delivered by faculty and reported as received by medical intensive care unit housestaff.

Methods: We performed a prospective cohort study in the University of Pittsburgh MICU. Faculty were enrolled in consecutive weeks as they rotated on and off service. The feedback was given to housestaff (residents and fellows on service). In phase 1, we sent a text at 5:00 pm asking faculty "Have you delivered feedback today?" and another asking the housestaff "Have you received feedback today." In phase 2, we sent the same texts to both faculty and housestaff and also gave the faculty a brief didactic and pocket card of a two-step method for giving feedback. In phase 3, we removed the faculty text message prompt, continued the didactic/pocket card and only asked the housestaff if they received feedback. The main outcome was the frequency of feedback reported by faculty and housestaff.

Results: We enrolled 39 housestaff and 14 faculty. With exclusion of those on nights, housestaff response rate was 79% (341/432). Faculty response rate was 100%. In phase 1 with text message delivery to both faculty and housestaff, faculty report of feedback delivery was 63% and housestaff report of feedback receipt was 46%. During phase 2 with text message and didactic delivery to faculty, faculty feedback delivery increased to 80% and housestaff report of feedback receipt was unchanged at 45%. In phase 3 with text message delivery only to housestaff and no text message prompt to faculty, housestaff report of feedback receipt decreased to 15%.

Conclusion: A brief faculty didactic improved rates of feedback delivery but did not change the rate that housestaff reported receiving feedback. A text message prompt to faculty had the largest impact on housestaff reports of receiving feedback.
Poster: Qualitative analysis of a Social Determinants of Health (SDH) Focused Home Visit Curriculum for Internal Medicine Residents

Presenter: Iman Hassan, Clinical Fellow

Research Interest: Medical Education
General Internal Medicine

Mentors: Maggie Benson MD

Funding Source: Thomas H. Nimick Jr. Competitive Research Fund

Authors: Iman Hassan MD, Amy Kennedy MD, Flor de Abril Cameron MPH, Megan Hamm PhD, Thuy Bui MD, Carla Spagnoletti MD, Maggie Benson MD

Introduction: Few categorical medicine residencies offer SDH curricula, despite its impact on health. We sought to enhance residents’ awareness of SDH via a home visit curriculum, which included a small-group session on neighborhood health effects, tools to address SDH, a virtual and physical neighborhood assessment and an SDH-focused home visit on a clinic patient.

Methods: We conducted 5-60-min focus groups of 3 to 5 residents within 2 weeks of the home visit. A total 19 residents participated. A trained facilitator guided the discussion using a question script. Sessions were audio-recorded and transcribed. A codebook was developed with a qualitative expert. Two coders independently applied codes to all transcripts using ATLAS.ti 8.0. Discrepancies were adjudicated until full agreement reached.

Results: (1) Residents reported the curriculum offered a unique, experiential opportunity to see how SDH impact health. A resident said, "you don’t have to imagine, you see it and then you realize ‘oh I should be thinking about xy and z’. This is more helpful than someone saying think about social determinants.” (2) Residents cited the neighborhood--mapping component of the virtual assessment as applicable to future patients. “The benefit...was to get us thinking about the patient in the context of his surroundings, rather than just in the context of his or her home” and in clinic “actually seeing how far away [the neighborhood] is from the clinic would probably inform my care a little bit better without taking any extra time.” (3) Residents felt the curriculum enhanced their conceptualization of SDH and offered concrete tools applicable to other patients. A resident said, “I think this entire exercise was useful in that now I feel like I know some resources better...feeling like I have something to offer them I think will increase the likelihood that I will bring these things up, with anybody.” Another said, “in my clinic after having done these, I do spend so much more time just being like, “Okay what neighborhood do you live in? Do you live in a house, an apartment?...I ask all sorts of weird questions that I didn't used to ask. Just because I do feel like it's helpful to have a better sense of who they are and where they are.”

Conclusion: Our curriculum prompted greater engagement with SDH among residents. They valued the experiential nature and identified components applicable to other patients. Neighborhood and home visits, with emphasis on local resources, can be successfully used to help residents incorporate SDH into clinical care.
Introduction: Grit is a personal characteristic, defined as passion and perseverance for long-term goals. It has been associated with success and avoidance of burnout in a number of fields outside of medicine. However, the relevance and validity of this construct among physicians has not been well established. We aimed to evaluate Grit among our first-year internal medicine residents in relation to burnout. Our hypothesis is that initial Grit level may help predict those who may be at highest risk of developing burnout.

Methods: We administered the well-validated Short Grit Scale (GRIT-S) and Maslach Burnout Inventory (MBI) to all PGY1 residents in Internal Medicine at the start of their training and again after 6 months. An additional background survey was administered to collect information on potential confounders, including age, gender identification, race, ethnicity, marital status, social supports, career goals, current rotation, work hours, daily exercise, and level of financial debt. Survey responses from the 6-month administration are still being collected. Initial levels of Grit and burnout were compared with levels of Grit and burnout at 6 months using paired Students t-tests with a 2-sided p-value<0.05 considered statistically significant. Additional analysis to control for confounders and elucidate any association between Grit and burnout using linear regression is planned.

Results: Among 75 PGY1 residents recruited, 49 have completed both the initial and 6-month surveys at this time. Two measures of burnout significantly increased, including both emotional exhaustion (p < 0.001) and cynicism (p < 0.001), while personal efficacy scores were unchanged (p = 0.56). Grit scores did not change (p = 0.32). Additional analysis is ongoing.

Conclusion: Our current analysis confirms that PGY1 residents are at high risk of developing burnout, particularly in the first 6 months of residency. Grit scores did not change over these six months. Whether this is due to the innate nature of Grit as a trait-level characteristic or the limitations of the GRIT-S is difficult to assess. Additional analysis is needed to determine if Grit is a helpful construct in this population.
101-B  **Poster:** Get S-M-A-R-T! Teaching Students Geriatric Health-Related Goal Setting

**Presenter:** Vivianne Oyefusi, Medical Student

**Research Interest:** Medical Education
Geriatric Medicine

**Mentors:** Rollin Wright MD

**Authors:** Vivianne Oyefusi BS, Pamela Toto PhD, Paula Leslie PhD, Rachel Jantea MD, Rollin Wright MD

**Introduction:** Goal-setting, particularly in geriatrics, is essential to person-centered care. It is linked to improved outcomes, quality of life and proactive health behaviors. While integral to training in some health professions, we suspected third year medical students (MS3) had not yet learned how to develop health-related goals. We piloted a tool to teach medical and other health sciences students how to develop health-related Specific-Measurable-Achievable-Realistic-Time-based (SMART) goals with community-dwelling older adults.

**Methods:** Health sciences students (including all MS3s), enrolled in an interprofessional geriatrics course sponsored by the University of Pittsburgh School of Medicine. They participated in a geriatric assessment skills fair (12 skills stations, 12 minutes each, skills cards) which prepared them for 9 community-based health fairs in Pittsburgh, PA. All students were required 1) to attend the SMART goals station where they learned how to develop health-related goals using the SMART criteria and 2) to develop at least 1 SMART goal working in teams of 2-3 with each health fair participant. Teams filled out 2 health assessment forms (1 copy to the participant, 1 copy for curriculum evaluation) on each participant and were instructed to write a SMART goal at the top of each copy. We graded the SMART goals according to the number of S-M-A-R-T criteria represented: D=attempted goal, 0 of 5, C=1 of 5, B=2 of 5, and A=3+ of 5 SMART criteria met.

**Results:** 200 health sciences students from 9 health professions schools participated in the 2018 course. Students turned in assessments of 209 participants. 104 forms (51.0%) contained 109 SMART goals. Of these, 21 (19.3%) goals received an A, 17 (15.6%) received a B, 28 (25.7%) were given a C, and 43 (39.4%) received a D grade. None of the goals achieved a perfect score, 5/5.

**Conclusion:** We designed a tool that successfully taught health sciences students to engage older people in person-centered, health-related goal-setting, a necessary skill for future careers in an environment that emphasizes high-value health care delivery. Further analyses will reveal which S-M-A-R-T criteria students found most challenging and guide improvements to the tool.
**Poster: A brief educational intervention improves primary care providers’ confidence and knowledge and affects clinical practice patterns for chronic obstructive pulmonary disease patients**

**Presenter:** Craig Riley, Clinical Fellow

**Research Interest:** Medical Education
- Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Jessica Bon MD

**Funding Source:** VA Medical Education/Patient Safety Award

**Authors:** Craig Riley MD, Sharon Camhi MD, Jessica Bon MD

**Introduction:** Chronic obstructive pulmonary disease (COPD) affects 30 million adults in the United States and is the 4th-leading cause of death. Many patients with COPD receive guideline-discordant care, with inhaled corticosteroids particularly overused. Furthermore, adherence to inhaled medications is poor, and few clinicians assess adequacy of patient inhaler use. As the majority of COPD care is delivered by primary care providers (PCPs), we sought to evaluate whether an educational intervention for PCPs could increase knowledge and confidence regarding inhaled pharmacotherapy, change prescription practices, or improve clinical outcomes.

**Methods:** We developed a 30-minute didactic on diagnosis and management of COPD according to the GOLD 2018 guidelines including hands-on inhaler demonstration which was delivered to primary care residents, fellows and attendings at the VA Pittsburgh University Drive in October and November 2017. The didactic was supplemented with educational handouts. We developed a survey incorporating Likert-type questions on COPD management and inhaler use to assess clinician confidence levels and guideline-adherent medication choices to assess knowledge; the survey was administered to participants prior to and 3 weeks after the didactic session. PCPs at VA Pittsburgh HJ Heinz filled out surveys and were given educational handouts to serve as a control for the didactic. Patient-level data were collected from the electronic record to assess inhaler training referrals, prescription patterns, and patient-centered outcomes pre- and post-intervention.

**Results:** Of the 75 University Drive PCPs, 76% attended the didactic intervention and completed surveys; 58% of these completed post-intervention surveys. 44% of the 18 HJ Heinz PCPs filled out surveys. For the intervention group, confidence and knowledge scores improved significantly following the intervention (confidence score 2.2 vs 3.9 out of 5, knowledge score 4.1 vs 5.1 out of 7, p < 0.05 for each). Patients at the intervention site were more likely to be referred for inhaler training (5.2% vs 1.4%, p < 0.0001) and less likely to use inhaled corticosteroids (36% vs 43%, p < 0.01) post- vs pre-intervention. Inhaler referrals and inhaled corticosteroid use did not differ between the pre- and post-intervention time periods at the control site. COPD exacerbation and pneumonia trends did not differ between sites.

**Conclusion:** A brief didactic including hands-on inhaler demonstration significantly increased PCP confidence and knowledge regarding guideline-based management of patients with COPD. Compared with educational materials alone, this intervention was associated with increased patient referrals for inhaler training and decreased use of inhaled corticosteroids but not with changes in clinical outcomes.
**Poster: Improving patient comprehension of dialysis modalities via in-patient education program for new start hemodialysis patients using iPad**

**Presenter:** Syeda Ahmad, Clinical Fellow

**Research Interest:** Quality Improvement
Renal-Electrolyte

**Mentors:** Ranil DeSilva MD

**Funding Source:** DOM - Renal Division/ QI committee

**Authors:** Syeda Ahmad MD, Huiwen Chen MD, Michael Donahoe MD, Filitsa Bender MD, Ranil DeSilva MD

**Introduction:** Dialysis education is done in outpatient setting and has been shown to improve survival rates. Few studies have examined dialysis education in advanced chronic kidney disease (CKD) patients starting dialysis during hospitalization. In the United States, patients who start dialysis inpatient are started on hemodialysis (HD). However, dialysis modalities such as peritoneal dialysis (PD) and home hemodialysis (HHD) offer better quality of life and outcomes. Thus, we sought to establish an inpatient dialysis education program for our advanced CKD to dialysis patients as a quality improvement initiative. The primary aim of our project is to improve patient understanding of dialysis modalities, chronic kidney disease, and dietary changes prior to discharge. Our secondary aim is to refine educational material and determine long term outcomes such as dialysis modality of choice.

**Methods:** We will enroll patients admitted to UPMC Magee-Women's, Presbyterian-Montefiore who are advanced CKD (stage 4/5), starting dialysis on their admission, and agreeable to dialysis education. The dialysis education will be provided on iPad by a physician (renal fellow) with links to UPMC health library and printed material from health library. Patients can choose to get additional educational support via tele-health video conference app with an outpatient renal dialysis education nurse. Patient response to dialysis education will be collected using survey. The average time for education and demographics (provided by patient) will be recorded along with patient preference for dialysis modality post education.

**Results:** The project was initiated in January 2019 with enrollment of 4 patients. The average age was 70 and 75% female. All patients had previously seen a nephrologist. The average time required for education was 45 minutes. All patients reported their post education understanding of dialysis and kidney disease as 5 (excellent) on scale of 1 to 5. Post education, 3 out of 4 patients were leaning towards HHD vs PD. One out of four patients used the online link to UPMC Health Library.

**Conclusion:** Preliminary results in on-going project are consistent with other studies which showed that with "modality-neutral counseling", patients have increased tendency to choose PD. The patient response has been positive, with patient reported improved comprehension of dialysis modalities and kidney disease. We hope that by increasing enrollment, we can better assess the effectiveness of our program and follow up with patients regarding dialysis modality. Based on our progress, we aim to refine methods into incorporating tele-health and non-physician as educator.
Poster Abstracts

105-B Poster: Medication use and adverse drug reaction evaluation in the peri-emergency endotracheal intubation period

Presenter: Simona Avramosvka, Graduate Student

Research Interest: Quality Improvement
   Pulmonary, Allergy and Critical Care Medicine Affiliated

Mentors: Phillip Lamberty MD

Authors: Simona Avramosvka BS, Phillip Lamberty MD, Sandra Kane-Gill PharmD, Pamela Smithburger PharmD

Introduction: This project aimed to identify adverse drug reactions (ADRs) during the peri-emergency endotracheal intubation (ETI) period and evaluate the use and appropriateness of physicians' choices of neuromuscular blocking agents (NMBA) and induction agents during emergency endotracheal intubation (ETI).

Methods: This was a single-center prospective analysis of 51 emergency ETIs conducted in an ICU at a large academic medical center. Qualifying patients were identified through an electronic alert generated by TherDoc when a medication order for an induction agent or an NMBA was placed in the medical or cardiac ICU. Included patients were screened for ADRs by using three causality assessment tools (Kramer, Jones, Naranjo). Severity of the ADR was classified using Common Terminology Criteria for Adverse Event published by the NIH (CTCAE). The modified MEDMARX was used to assess the amount of harm caused by the ADR to the patient. Hemodynamic outcomes of the emergency ETI (SpO2 <88 percent or SBP <70 mmHg) were compared based upon NMBA use. Data were described using descriptive statistics and analyzed with a Fisher's exact test.

Results: Fifty-one intubations were evaluated. Eight ADRs were identified during the peri-intubation period. Two transpired during intubation as a result of the induction agent chosen and six occurred post-intubation as a result of initial sedation chosen. All ADRs resulted in a medically significant event as based on the NIH (CTCAE). All ADR's received a MedMARX rating of at least "D" (medication reached the patient and required monitoring to confirm that it resulted in no harm and or required intervention to prevent harm). Of the 51 intubations, a NMBA was used 74.5% (38/51) of the time. Dosing of the NMBA was appropriate in 84.2% (32/38) of intubations based upon patient weight. Upon comparison of hemodynamic outcomes of emergency ETI based upon NMBA use, there were no differences in desaturations (SpO2 <88 percent) (p=0.67) or hypotension (SBP <70 mmHg) (p=0.33) between the patients that received a NMBA and those that did not.

Conclusion: As post-intubation sedative agents accounted for two thirds of the identified ADRs, additional education on medication selection and dosing is needed to decrease potential ADRs. A larger evaluation is needed to further elucidate ADR incidence in the peri-emergency ETI period and the impact of NMBA use on patient hemodynamic outcomes.
**106-B  Poster: Increasing Care Engagement amongst People Living with HIV through a Text Messaging Intervention**

**Presenter:** Nupur Gupta, Clinical Fellow

**Research Interest:** Quality Improvement  
Infectious Diseases

**Mentors:** Sarah McBeth MD

**Authors:** Nupur Gupta DO, Sarah McBeth MD, Ella Kaplan LCSW, Becky McDermott MSW, Linda Despines RN, Deborah McMahon MD

**Introduction:** HIV has transitioned from an acute, life-threatening illness to a chronic disease. Management has transformed due to potent antiretroviral therapy (ART) which led to a decrease in morbidity and mortality among people living with HIV (PLWH). But, PLWH must be compliant with a daily medication regimen and maintain medical care which is difficult due to multiple barriers. The HIV care continuum was developed as a series of steps that PLWH take in their treatment cascade and pinpoints the gaps. The continuum was incorporated into global, national, and local initiatives to increase the proportion of people at each step. At the HIV clinic, 90% of the patients are virally suppressed (viral load < 200 copies/ml). Although this is higher than the national average, some patients face challenges with consequential clinical and public health implications.

**Methods:** The aim is to demonstrate that a text messaging-based intervention will increase the proportion of PLWH along the care continuum including those who are retained in care, prescribed ART and virally suppressed. The pre-intervention dataset consists of the clinic population with a viral load greater than or equal to 200 copies/ml between 7/1/2017-6/30/2018. After the initial chart review, eligible patients will be consented to receive weekly text messages with content regarding appointment and medication reminders and motivational messages. In the group receiving text messages, effectiveness of the intervention will be measured by tracking their appointments, viral loads, and ART prescriptions.

**Results:** 125 patients were identified based on the inclusion criteria. Initial chart review excluded 44 and thus 80 patients are eligible for the intervention. In the eligible group, the average age is 40.1 years old, 68% are males, and 68% are African-American. The average length of care at PACT is 8 years (range 0 to 26 years) and average number of years since initial ART prescription is 6.8 years (range 0 to 20 years). The average viral load is 27,372 copies/ml. The most common barriers were: mental health, communication, and insurance.

**Conclusion:** The intervention is currently enrolling with weekly text messages being sent to the patients that are eligible and consented. The most prominent barrier in this study is the consent process. If the text messaging intervention demonstrates effectiveness, then we can improve outcomes and impact the regional HIV care continuum in order to reach the year 2020 targets. This pilot intervention can also help determine if this is a viable method to link other at-risk patients to care.
107-B  **Poster:** Addressing Sexual Health Needs of Cancer Survivors: a Psychiatrist's Perspective

**Presenter:** Shelly Kucherer, Clinical Fellow

**Research Interest:** Quality Improvement  
Other

**Mentors:** Robin Valpey MD

**Authors:** Shelly Kucherer MD, Robin Valpey MD

**Introduction:** Cancer survivors are living longer, placing increasing emphasis on survivorship care. Sexual health is an important aspect of care, as prevalence of sexual dysfunction in survivors is high, with some studies citing up to 100% of breast cancer patients reporting sexual dysfunction after diagnosis. Sexual health concerns are multi-factorial including anatomic and hormonal changes, treatment effects, pain, body image issues, and psychiatric pathology. While studies show cancer patients want to discuss sexual concerns, these issues often go undiscussed. To our knowledge, no studies have looked at how psychiatrists talk to cancer survivors about sexual health.

**Methods:** We developed a survey for psychiatrists who treat patients with both psychiatric and oncologic concerns. We collected data on provider’s comfort in assessing sexual side effects from medications, ease in talking to patients about sexual health, and confidence in diagnosing the cause of sexual health problems. Additionally we assessed psychiatrist’s knowledge about sexual health issues in this population.

**Results:** We found that all 12 psychiatrists who completed the survey talked to their patients about medication side effects, but 33% reported talking about sexual side effects only “rarely.” While all recognized the importance of having comfort with this topic, factors making this more difficult include patient-provider differences in gender and age, as well as provider comfort. While most physicians were able to state some of the most common sexual side effects from psychiatric medications, they were less confident in differentiating the cause of sexual dysfunction in those with cancer (mean confidence level 0.625). All providers were interested in learning more about sexual health issues in cancer.

**Conclusion:** Preliminary results show psychiatrists have a good understanding of sexual side effects from psychiatric medications, but less about sexual side effects from cancer. Given this identified need and reported interest, education for psychiatrists on diagnosing and treating sexual health concerns in the psycho-oncology population is a possible intervention to benefit cancer patients with sexual issues. Given the high prevalence of sexual dysfunction in cancer survivors, psychiatrists have a unique ability to help fill the need for identifying and treating these concerns.
Introduction: Diabetes mellitus type 2 management has experienced an evolution with the addition of novel anti-diabetic agents such as GLP-1 agonists and SGLT2 inhibitors, but metformin remains first-line in the current guidelines. Metformin is not only a cost-effective option for the treatment of diabetes but has been shown to improve mortality and glycemic control without the risk of hypoglycemia or weight gain. Since its approval in 1994 there have been updates to the FDA labeling. In 2006, heart failure was removed as a contraindication and in 2016 its use in renal dysfunction was clarified. Heart failure, hepatic impairment, age, alcohol use, and stress-related states are still listed as concerns by the FDA, but there is evidence to suggest that metformin use is both safe and beneficial in the setting of many of these risks. The goal of this project is to evaluate metformin usage and discontinuation in a real life setting to help ensure maximal utilization for this cost-effective and life-saving first-line agent.

Methods: A Retrospective analysis of patient with type 2 diabetes in the VA Pittsburgh Healthcare System approved as a review of clinical operation. The study population was formulated using pharmacy records for the past 5 years to identify patients prescribed any non-insulin anti-diabetic agent. The primary endpoint was to determine reasons for metformin discontinuation. Progress notes, allergy lists, problem lists, lab results, and other data gathered by chart review were used to identify reasons for discontinuation and relevant comorbidities. Appropriate reasons for discontinuation were defined as those with heart failure and reduced EF <40% or multiple admissions for CHF, GFR <45, Childs B or C hepatic impairment, oxygen prescription, intolerance, and significant medication interactions.

Results: The study is ongoing and to date 1,481 patients have been identified through pharmacy records. Thus far 17% of charts have been reviewed. Of those reviewed, 81% of those patients are on metformin when GFR is accounted for. Of those previously on metformin, 25% were deemed to have been inappropriately discontinued or found to not have any contraindication for use.

Conclusion: No formal conclusions have been determined as the study is not complete though the concern is that metformin is underutilized and common reasons for discontinuation are intolerance, reduced renal function, heart failure or hepatic impairment. Identifying the appropriateness of discontinuation will help aid providers in maximizing metformin usage.
**109-B Poster:** Back table perfusate fluid culturing does not reduce infections or mortality in liver transplant patients, and leads to increased antimicrobial usage.

**Presenter:** Peter Volpe, Clinical Fellow

**Research Interest:** Quality Improvement
Infectious Diseases

**Mentors:** Brooke Decker MD

**Authors:** Peter Volpe MD, Brooke Decker MD, Neil Clancy MD, Deanna Buehrle PharmD, M.Hong Nguyen MD

**Introduction:** Culturing back table perfusate fluid to portend infections following liver transplantation is controversial. Limited data do not suggest that treating positive perfusate cultures reduces surgical site (SSIs) or peri-transplant infections. Moreover, the impact of performing perfusate cultures on antimicrobial usage and stewardship is unknown.

**Methods:** We implemented routine surveillance culturing of perfusate fluid in 2015. Liver transplant recipients from March 2015 to June 2018 were reviewed.

**Results:** Perfusate cultures were performed in all 131 liver transplant recipients, 21.4% (28/131) of which were positive. The most common organisms isolated were coagulase negative Staphylococcus (35.7%), Enterobacteriaceae (32%), and Candida spp. (25%). Sixty-one percent (17/28) of positive cultures were treated with organism-directed antimicrobials, for median 13 days (range: 1 to 51). Patients in whom positive cultures were not treated received median 0 days (range: 0 to 35 days) of antimicrobials (P=0.005). No peri-transplant infections were caused by organisms identified in perfusate cultures. There were no differences in Clostridioides difficile (12% (2/17) vs 9% (1/11), P=1.0), MDRO (0% (0/17) vs 18% (2/11) p=0.14), or SSIs (6% (1/17) vs 0% (0/11), P=1.0) among patients treated or not treated for positive perfusate cultures, respectively. Likewise, differences were not observed in infections within 2 weeks (35% (6/17) vs 9% (1/11), P=0.19), 1 month (12.5% (2/16) vs. 9% (1/11), P=1), or 3 months (0% (0/16) vs. 9% (1/11), P=0.41) post-transplant among patients in whom positive cultures were treated or not treated, respectively. There was no difference in SSIs in patients with positive vs negative perfusate cultures (4% (1/28) vs 3% (3/102), P=1.0). Patients with negative perfusate cultures had shorter post-transplant median length of stay than those with positive cultures (14 days vs 18.5 days, P=0.03). There was no difference in all-cause 90-day mortality between patients with positive 7% (2/28) and negative 3% (3/103) cultures (P= 0.29).

**Conclusion:** Perfusate culture positivity is common among liver transplant recipients. However, neither culture positivity nor antimicrobial treatment of positive cultures was associated with reductions in C. difficile infections, MDRO infections, SSIs, any infections, or mortality. Rather, patients in whom positive cultures were treated received significantly longer courses of antimicrobials, and patients with positive cultures had significantly longer lengths of stay. Therefore, there were no apparent benefits to performing perfusate cultures, and the practice may have had a deleterious impact on antimicrobial consumption and lengths of stay.
**Poster Abstracts**

**110-B Poster:** Effect of Sacubitril/Valsartan on Right Ventricular Function in Pulmonary Hypertension

**Presenter:** Evan Benza, Research Associate

**Research Interest:** Translational Cardiology

**Mentors:** Marc Simon MD

**Funding Source:** Novartis Pharmaceuticals Corporation

**Authors:** Evan Benza BS, Timothy Bachman MS, Danial Sharifi MSc, Claire Tushak, Kang Kim PhD, Marc Simon MD

**Introduction:** Right ventricular failure is the main cause of mortality in pulmonary hypertension (PH). The initial response of the right ventricle to the increased vascular load seen in PH is to increase RV contractility, which leads to myocardial hypertrophy, RV dilation and eventual decreased RV contractility and RV failure. Sacubitril/Valsartan (Sac/Val) is an angiotensin receptor blocker (ARB) combined with a neprilysin inhibitor. Sac/Val has a synergistic effect on vasodilation, blood pressure reduction, and inhibition of hypertrophy and fibrosis, which improves outcomes in systolic left ventricular failure. We are studying the effects of preventive treatment of PH with Sac/Val on the failing RV using an experimental model of PH.

**Methods:** Sprague Dawley rats were studied in 4 groups: Controls (n=8), PH with placebo treatment (n=5), Valsartan only treatment (n=4), and Sac/Val treatment (n=7). PH was induced via pulmonary artery banding (PAB). Sac/Val, Val, or placebo was administered daily via oral gavage. At three weeks post-surgery, terminal invasive hemodynamic measurements were performed to obtain pressure-volume (PV) loops with vena cava occlusion using a conductance catheter system (Millar, Inc, Houston, TX) then analyzed with LabView Software v.4.x (National Instruments, Austin, TX). Following hemodynamic measurements, the heart was removed and the RV tissue underwent biomechanical testing. Herein, we report the preliminary hemodynamic findings. Statistical analysis was performed using Kruskal-Wallis with Dunn post-hoc analysis or Mann-Whitney tests (SPSS v. 24, IBM, Armonk, NY). Data expressed as mean ± SEM.

**Results:** PAB resulted in significantly elevated RV systolic pressure (58 ± 5 vs control 25 ± 1 mmHg, P=0.002). Sac/Val significantly reduced RV systolic pressure (41 ± 5 mmHg, P=0.03, vs PAB) while Val only did not (51 ± 8 mmHg, P=0.5). RV Volumes increased with PAB and there was no effect of treatment and no change in stroke volume. There was no change in contractility as measured by the gold standard end-systolic elastance (Ees) although dP/dtmax trended to increase in all groups vs control (P=0.07). Ventricular-vascular coupling (Ees/Ea) was unchanged.

**Conclusion:** Sac/Val significantly reduced RV systolic pressure and may be a potential therapy for PH and RV dysfunction. This study is ongoing with further work studying RV remodeling and tissue biomechanics. If positive, as suggested by these preliminary data, a clinical trial may be warranted.
Poster: Triptolide May Improve Graft Quality During Ex Vivo Lung Perfusion Leading To Better Posttransplant Outcomes

Presenter: Sarah Burki, Post-Doctoral Fellow

Research Interest: Translational
Cardiology Affiliated

Mentors: Jonathan D’Cunha MD PhD

Funding Source: Departmental support

Authors: Sarah Burki MD, Kentaro Noda PhD, Brian Philips PhD, Ajay Kumar PhD, Pablo Sanchez MD, PhD, Jonathan D’Cunha MD PhD

Introduction: Lung transplantation is the only therapeutic option for many patients with end stage lung disease, yet posttransplant outcomes remain suboptimal. Ex vivo lung perfusion (EVLP) has the potential to increase the lung donor pool. However, de novo inflammation may be induced in grafts during EVLP, augmented by activated metabolism at normothermia thereby affecting graft quality. Graft inflammation has been associated with development of short and long term posttransplant complications, such as primary graft dysfunction and chronic lung allograft dysfunction which negatively impact survival. Triptolide, a diterpenoid triepoxide having inhibitory effect for Nuclear Factor-kB (NF-kB) signaling, has been shown to have a therapeutic potential in various disease states. We hypothesized that Triptolide may inhibit graft inflammation induced during EVLP leading to improved posttransplant graft function. Therefore, the aim of this study is to assess the effect of Triptolide on graft quality during EVLP through inhibiting an inflammatory pathway, as well as on graft condition after transplant using a rat model.

Methods: Using rat heart-lung blocs, EVLP was performed with Steen solution with (and without) 100 nM of Triptolide at 37°C for 4 hours. Graft evaluation during EVLP included physiologic, metabolic and functional parameters. Tissue inflammatory profile and endoplasmic reticulum stress were assessed by real-time reverse transcription polymerase chain reaction (RT-PCR) and Western Blot in tissue after 4 hours EVLP. Nuclear factor-kB (NF-kB) DNA binding, indicating activation of inflammatory pathway, was assessed by chromatin immunoprecipitation (ChIP). After EVLP, orthotopic single lung transplantation using 3-cuff technique in syngeneic recipients was performed, and the graft was reperfused for 2 hours. The graft was evaluated in terms of function and inflammation.

Results: Dynamic compliance, pulmonary vascular resistance, and PaO2/FiO2 of lung grafts on EVLP with Triptolide were significantly better than control. Lungs treated with Triptolide showed significantly lower glucose consumption compared to that without Triptolide. ChIP analysis revealed inhibited NF-kB binding to DNA, resulting in decreased downstream messenger RNA levels of proinflammatory cytokines confirmed in tissue after 4 hours of EVLP with Triptolide. Triptolide significantly reduced the protein expression of C/EBP homologous protein in tissue after EVLP compared to control. Most importantly, posttransplant PaO2/FiO2 and inflammation were significantly better in the Triptolide group compared to control.

Conclusion: Inhibition of de novo inflammation using Triptolide during EVLP may have a potential to improve graft condition during EVLP thus leading to potentially better posttransplant outcomes.
113-B Poster: Regional Homogeneity analysis of the brain's role in bladder filling

Presenter: Becky Clarkson, Junior Faculty

Research Interest: Translational Geriatric Medicine

Authors: Becky Clarkson PhD, Helmet Karim PhD, Neil Resnick MD

Introduction: The brain plays a vital role in the continence mechanism. We have built our understanding of this upon a series of statistical analyses of activity during bladder-related tasks; these findings can be challenging to interpret and envisage, particularly for a non-neuroimaging audience. We sought to find a way to represent brain activity information that would intuitively represent a bladder task, such as filling. We present an analysis of bladder filling in an MRI scanner, from empty until strong desire to void, using 'Regional Homogeneity' (ReHo) which assesses regional brain activation. ReHo evaluates similarity of activation of each voxel with its nearest neighbors, producing a map of activation over time which emphasizes robust clusters of activation. This can be displayed as a time-lapse video of regional activation over the course of bladder filling to visualize brain function in response to stimulus.

Methods: Nine women over 60 years of age with urgency urinary incontinence (UUI) >5x/week underwent bladder filling at 50ml/minute until strong desire to void, while having a BOLD fMRI scan. ReHo was calculated for each voxel in the brain by calculating Kendall’s coefficient concordance (KCC) between neighboring voxels (any voxel touching a vertex; 27 voxel neighborhood), which measures similarity between that voxel and its neighbors. More concordant regions are more likely to have co-activated. We computed this over a sliding window of 20 data points allowing visualization as a function of time. We computed the average time series across participants and visualized ReHo at the supplementary motor area (SMA). We calculated ReHo at the last quartile of filling time and compared it to the initial three quartiles in each participant using a paired t-test to quantitatively assess activation changes.

Results: A video shows changes in ReHo occurring concurrently bladder filling. The SMA activity increases towards the end of filling. Quantitatively, mean ReHo in the SMA (MNI 2 0 48) was greater at the last 25% of the filling (mean=0.19, SD=0.01) compared to the first 75% of the filling (mean=0.17, SD=0.02) with t(9)= -2.44, p<0.05 (95% confidence interval [-0.028, -0.011]).

Conclusion: Time-lapse video provides a way to qualitatively assess brain function over time in response to bladder filling; providing context and visualization to brain-bladder studies. The video shows the SMA, known to be involved in urgency, acts as expected. We aim to use this method to quantitatively assess activity, improve visualization and contextualize our data in future.
**Poster: Rectal swabs in critically-ill patients provide discordant representations of the gut microbiome compared to stool samples: a brief methodologic report.**

**Presenter:** Katherine Fair, Medical Student

**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Georgios Kitsios MD PhD

**Authors:** Katherine Fair AB, Daniel G. Dunlap MD, Adam Fitch MS, Allison Morris MD MS, Bryan McVerry MD, Georgios Kitsios MD PhD

**Introduction:** K23

**Methods:** The role of the gut microbiome in critical illness is being actively investigated, but the optimal sampling methods for sequencing studies of gut microbiota remain unknown. Stool samples are generally considered gold-standard but are not practical to obtain in the intensive care unit (ICU), and thus, rectal swabs are often used. However, the reliability of rectal swabs for gut microbiome profiling has not been established in this clinical setting.

**Results:** In this study, we compared 16S rRNA gene sequencing results between rectal swab and stool samples collected at three timepoints in mechanically-ventilated critically-ill adults admitted to the MICU at UPMC Presbyterian Hospital. Sequencing data were analyzed for alpha and beta diversity and taxonomic composition with the R software.

**Conclusion:** Rectal swabs comprised 89% of samples collected at the baseline timepoint, but stool samples became more available at later time-points. Significant differences in alpha and beta-diversity between rectal swabs and stool samples were observed (p<0.003), but these differences were primarily due to baseline samples. Higher relative abundance of Actinobacteria phyla (typically skin microbes) was present in rectal swabs compared to stool samples (p<0.02), a difference that was attenuated overtime.
Poster Abstracts

115-B Poster: Sensitive Next-Generation Sequencing of HIV-1 from Seroconverters in the MTN-020/ASPIRE Dapivirine Vaginal Ring Study

Presenter: Breanna Goetz, Research III

Research Interest: Translational Infectious Diseases

Mentors: Kerri Penrose MS

Funding Source: MTN is funded by the NIAID

Authors: Urvi Parikh PhD, Amy Heaps MS, Kerri Penrose MS, Rahil Sethi MS, Jacob Waldman MS, Valerie Boltz MS, Breanna Goetz BS, Daniel Szydlo, Marla Husnik, Uma Chandran PhD, Thesla Palanee-Phillips, Jared Baeten, John Mellors PhD

Introduction: A concern about dapivirine (DPV) for HIV prevention is resistant virus selection with breakthrough infection, including low frequency resistant variants missed by standard genotype that could promote spread of NNRTI resistance or reduce effectiveness of NNRTI-based 1st-line ART. We evaluated seroconverters in MTN-020/ASPIRE using sensitive next-generation sequencing (NGS) for drug resistance associated with DPV ring use.

Methods: ASPIRE was a safety and effectiveness study of the DPV intravaginal ring for HIV prevention conducted at 15 sites in South Africa, Zimbabwe, Malawi and Uganda. Plasma for NGS was collected at the 1st positive rapid HIV-1 test prior to ring discontinuation. Of 71 DPV arm seroconverters, 63 had detectable plasma DPV and HIV-1 RNA >350 c/ml. Plasma from these 63 was tested, along with matched controls from the placebo (PLB) arm, using NGS with unique molecular identifiers targeting HIV-1 RT aa 81-149 and 152-212. Drug resistance mutations (DRM) were defined by 2017 IAS-USA and reported if their frequency was =1%.

Results: 58 DPV and 57 PLB arm seroconverters were successfully tested by NGS. Overall, 13/115 (11%) had NNRTI DRM detected including V90I, K101E, K103N/S, V106M, V108I, E138A/G and V179D/T. Only 1 sample (PLB ring) had a low frequency DRM detected (9% E138A) that was missed by standard genotyping. The frequency of NNRTI DRM did not differ significantly by arm: 8/58 (14%) DPV arm vs. 5/57 (9%) PLB arm; p=0.41 (Chi-Square). Mutations selected by DPV in vitro including L100I, E138K, V179F or Y181C/I were not detected, even at low frequency.

Conclusion: NGS of HIV-1 in plasma samples at seroconversion in MTN 020/ASPIRE showed no significant difference in NNRTI DRM frequency between the DPV and PLB arms. Low frequency NNRTI DRM missed by standard genotype were rare in either arm. These findings indicate that NNRTI-resistant HIV was not preferentially transmitted or selected by the DPV ring and that the preventive benefit of the DPV ring outweighs drug resistance risk.
**Poster: Ultrasound-mediated antitumor efficacy of liposomal doxorubicin conjugated polymer microbubbles with reduced cardiotoxicity in a mouse model of soft tissue sarcoma**

**Presenter:** Mingyu He, Post-Doctoral Associate

**Research Interest:** Translational VMI

**Mentors:** Flordeliza Villanueva MD

**Funding Source:** R21

**Authors:** Mingyu He PhD, Xucai Chen PhD, Flordeliza Villanueva MD

**Introduction:** Doxorubicin (Dox) is one of the most widely used chemotherapeutic agents and is standard of care for the treatment of sarcomas and other cancers. Unfortunately, Dox also induces cardiac damage in a dose-dependent manner. Pegylated liposomal Dox (Doxil®) putatively reduces cardiotoxicity. However, in clinical trials, Doxil® did not improve the maximal tolerated dose and caused a new dose-limiting toxicity, palmar-plantar erythrodysesthesia (PPE). Microbubbles (MBs) are intravenously injectable gas-filled contrast agent and suitable drug carriers that can prolong the half-life of the therapeutic substances and undergo disease site-specific ultrasound (US)-triggered unloading of cargo via navigation of the US beam. In this study, we developed polymer MBs carrying liposomal Dox with US-targeted microbubble cavitation (UTMC) directed at the tumor site to inhibit tumor growth in a murine sarcoma model while reducing cardiotoxicity.

**Methods:** Dox lipopolyplexes (DoxLPX) were developed. Liposomal Dox was conjugated to polymer MBs via biotin-avidin interaction. C57BL/6 mice with xenograft sarcoma tumors 40-90 mm³ in initial size (MCA205) were randomly assigned to 1 of 6 treatment groups: (1) free Dox; (2) liposomal Dox (Ldox); (3) DoxLPX; (4) MB+LDox co-injection; (5) empty liposomes (ELPX); or (6) saline. 360 µL of each formulation (first 4 Dox formulations containing 100 µg Dox or equivalent dosage; MB dose for DoxLPX, MB+LDox, and ELPX was 140 million MBs) were intravenously administered through a chronic indwelling jugular venous catheter. Concurrent US was delivered using a transducer fixed over the tumor. Treatment was given every 3 to 4 days (total 4 treatments). Tumor volume and cardiac function were serially monitored with high-resolution US imaging. Myocardial fibrosis in DoxLPX + US-treated animals were compared with that from control hearts.

**Results:** Compared to free Dox and liposomal Dox, DoxLPX + US treatment inhibited tumor growth rates and increased median survival time. Intravenous co-administration of MB and LDox + US inhibited tumor growth, but the magnitude was more variable. DoxLPX + US attenuated adverse effects of Dox on cardiac function; i.e., fewer animals had a decline in ejection fraction, fractional shortening, or an increase in left ventricle mass, and histologic analysis showed less myocardial collagen deposition compared to the other Dox-treated groups.

**Conclusion:** DoxLPX-loaded MBs combined with US targets doxorubicin delivery to the tumor site, resulting in tumor growth inhibition equivalent to that achieved by free Dox and with relative sparing of cardiotoxicity.
**Poster: Airway Transcriptome Analysis of the Lung Allograft Reveals Novel Immune Signatures in Chronic Lung Allograft Dysfunction**

**Presenter:** Carlo Iasella, Junior Faculty

**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine Affiliated

**Mentors:** John McDyer MD

**Funding Source:** Cystic Fibrosis Foundation

**Authors:** Carlo Iasella PharmD, Aki Hoji PhD, Mark Brown BS, Kong Chen PhD, John McDyer MD

**Introduction:** Chronic lung allograft dysfunction (CLAD) is the major limitation to long-term survival in lung transplant recipients (LTRs). The underlying biologic mechanisms that drive CLAD are poorly understood. To address the pathogenesis of CLAD at the molecular level, we performed RNA-seq analysis of airway brush samples in bronchial lavage (BAL) samples.

**Methods:** Total RNA was extracted from distal bronchial brush samples and sequenced using an Illumina instrument to obtain bulk RNA-seq data which were subsequently analyzed for differential gene expression (DGE) profiling with correction for a potential batch effect. Gene enrichment and gene and cell ontology analyses of DGE profile was done and used to predict canonical pathways and cellular upstream regular of activated signal pathways. False discovery rate (FDR) p<0.05 distinguished significantly overrepresented expression in CLAD samples. For upstream regulator analysis, a z-score above 2.00 with p<0.05 was significant. BAL from corresponding LTRs were subject to the multiplex MSD cytokine and chemokine array. Mann-Whitney U test was used and any analytes with p<0.05 was considered to be significant.

**Results:** 21 CLAD and 18 stable control LTRs were included for RNA-seq analysis. Corresponding MSD measurements were performed on 17 CLAD and 11 control BAL samples. 1031 DEGs were overrepresented in CLAD samples. Gene analyses revealed enrichment of the Type-1 adaptive immune response and the inflamasome. TNF-α (p<1.09E-41), IL-1β (p<5.24E-40), IL-1α (p<8.71E-24), STAT1 (p<7.96E-31), and IFN-γ (p<7.07E-45) were identified as key immune pathways upregulated in CLAD.

**Conclusion:** Transcriptome analyses in the lung allograft, provide novel insights into the immune activation pathways prevalent in CLAD versus controls. Further analyses may provide the rationale for testing select immune targets in CLAD and uncover distinct immune endotypes within CLAD.
**Poster**: Clinical Translation of Sonoreperfusion Therapy for Treatment of Microvascular Obstruction

**Presenter**: Filip Istvanic, Medical Student

**Research Interest**: Translational Cardiology

**Mentors**: John Pacella MD

**Funding Source**: HHMI, NIH, Physician Scientist Training Program

**Authors**: Filip Istvanic BS, Gary Yu BS, Francois Yu PhD, Jeff Powers PhD, Xucai Chen PhD, John Pacella MD

**Introduction**: Microembolization during percutaneous coronary intervention for acute myocardial infarction causes microvascular obstruction (MVO). We have shown that sonoreperfusion therapy using ultrasound (US) and microbubbles restores microvascular perfusion in an in vitro model of MVO, and that reperfusion efficacy increases with US pulse length and with US acoustic pressure. In enhance clinical translation of this technique, we compared the reperfusion efficacy of an experimental US system (modified Philips EPIQ) capable of long US pulses to that of a clinical US system (Philips Sonos 7500) with short US pulses in a rat hindlimb model of MVO.

**Methods**: Our rat hindlimb model of MVO was created by injecting microthrombi into the arterial circulation of the hindlimb muscle. Lipid encapsulated microbubbles were infused while therapeutic US was delivered to the obstructed microvasculature for 20 min using one of four ultrasound conditions: Sonos single-frame, Sonos multi-frame, EPIQ low pressure, and EPIQ high pressure. Control rats were injected with microthrombi but did not receive US therapy. Contrast enhanced US perfusion imaging of the microvasculature was conducted at three timepoints: baseline (BL), 10 min after microthrombi injection (MVO), and post-treatment (Tx). Microvascular blood volumes (MBV) were calculated from video intensity-time data measured in hindlimb muscle regions of interest.

**Results**: MBV was similar across all experimental groups at BL and at MVO. Data are expressed as mean ± SD. In the Sonos single-frame group (n=6), MBV increased to 25% of BL after Tx (5.0 ± 6.1 dB). In the Sonos multi-frame group (n=8), MBV increased to 51% of BL after Tx (9.3 ± 9.5 dB). In the EPIQ low pressure group (n=10), MBV increased to 46% of BL after Tx (9.7 ± 10.8 dB). In the EPIQ high pressure group (n=7), MBV increased to 93% of BL after Tx (17.0 ± 7.3 dB). In the control group (n=8), MBV remained reduced at 5% of BL after Tx (0.7 ± 0.8 dB). Two-way repeated measures ANOVA resulted in significant time, treatment, and interaction effects (p < 0.005). Tukey's post-hoc analysis within individual treatment groups across different timepoints showed that only the EPIQ high pressure group restored perfusion to BL after Tx (p < 0.05).

**Conclusion**: These data demonstrate the superior reperfusion efficacy of a long pulse, high pressure US delivery system. This work should inform clinical translation and optimization of sonoreperfusion of MVO.
**Poster Abstracts**

**119-B  Poster:** Oral microbiome community composition and metabolism of nitrate to nitrite are driven by individual differences with time.

**Presenter:** Carl Koch, Junior Faculty

**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** K24, P01, F32, and T32

**Authors:** Victoria Heinrich, Rachel Nettles, Shulin Qin, Courtney Sparacino-Watkins, Kelvin Li, Barbara Methe PhD, Adam Fitch, Alison Morris MD

**Introduction:** The oral microbiome has been implicated in systemic nitric oxide (NO) homeostasis via the unique ability of specific bacteria to enzymatically bioactivate inorganic nitrate to nitrite, NO and other vasoactive nitrogen oxides. Ongoing work suggests that alterations in oral microbial nitrate reduction may contribute to the pathophysiology of pulmonary- and cardio-vascular diseases and represent a novel target for therapeutic or prognostic interventions. However, little is known about the individual and temporal variation in oral microbial communities, and even less about variation in nitrate metabolism. We therefore studied the structure and nitrate-reducing capacity of the oral microbiome in a population of healthy individuals over time.

**Methods:** Oral wash samples were collected from 10 healthy, non-fasting volunteers twice daily over the course of three consecutive days. 16S rRNA bacterial gene sequencing of the V4 variable region was performed on the Illumina MiSeq platform and analyzed for community composition using the analytic software Calypso and R. Microbial nitrate reductase enzyme activity was measured using an in vitro functional assay and gas phase chemiluminescence. Compositional changes were compared by individual, time of day, and across days using permutational and repeated measures analysis of variance (PERMANOVA).

**Results:** Within-individual, Shannon diversity significantly differed by subject (R2=0.701, p<0.0001) and by subject by day (R2=0.765, p=0.003). Between-individual, Bray-Curtis dissimilarities also differed by subject (R2=0.691, p=0.0003), subject by day (R2=0.833, p=0.0003), and subject by time-of-day (R2=0.814, p=0.0003), as well as by time-of-day (R2=0.056, p=0.018). Nitrate-reducing capacity was estimated by calculating the log-ratio of taxa with known high nitrate-reducing activity (Veillonella, Rothia, Haemophilus, Actinomyces, and Lactobacillus) to taxa with known low nitrate-reducing activity (Porphyromonas, Fusobacterium, and Leptotrichia). Again, nitrate-reducing capacity significantly differed only by subject (R2=0.665, p<0.0001) and by subject by day (R2=0.762, p=0.0003).

**Conclusion:** In the oral wash of healthy individuals, approximately 70% of the variation in the diversity of the oral microbiome is explained by individual differences, with 6-14% additionally explained by individual variability across days of testing or by time of day. Further, individual variability also explained over 66% of differences in estimated nitrate-reducing capacity, with <10% additionally explained by individual variation across days of testing. Changes in the oral microbiome and its ability to reduce nitrate to nitrite vary by individual and remain largely stable with time and may be reasonable targets for individual therapeutic or prognostic interventions. Confirmatory assessment of quantitative enzymatic nitrate reduction activity remains on-going.
**Poster Abstracts**

**120-B  Poster:** Non-canonical HIPPO-MST1/2 supports pro-proliferative/pro-survival vascular smooth muscle phenotype and established pulmonary hypertension via modulating Akt1 and FoxO1

**Presenter:** Tatiana Kudryashova, Post-Doctoral Fellow

**Research Interest:** Translational VMI

**Mentors:** Elena Goncharova PhD

**Funding Source:** NIH/NHLBI

**Authors:** Tatiana Kudryashova PhD, Arnab Ray Undergraduate Student, Analise Rode BS, Yuanjun Shen PhD, Theodore Avolio BS, Dmitry Goncharov MSc, Yutong Zhao MD/PhD, Elena Goncharova PhD

**Introduction:** Increased proliferation and survival of pulmonary arterial vascular smooth muscle cells (PAVSMC) are important components of pulmonary vascular remodeling, a key pathological feature of pulmonary arterial hypertension (PAH). We recently reported that LATS1, a member of HIPPO growth-suppressor pathway, acts as a negative regulator of proliferative, apoptosis-resistant PAVSMC phenotype in PAH. The role of other key protein-kinases of HIPPO cassette, MST1/2, in PAH remains unknown.

**Methods:** Western blot, Immunocytochemistry, Immunohistochemistry, Cell proliferation/apoptosis assays, SuHx-mouse model of PH.

**Results:** siRNA-induced knockdown of MST1 or MST2 in early-passage distal PAVSMC from non-diseased (control) lungs increased proliferation and reduced levels of pro-apoptotic protein Bim, demonstrating canonical anti-proliferative/pro-apoptotic role for MST1/2. Surprisingly, in human PAH PAVSMC, siRNA MST1 and siRNA MST2 suppressed proliferation, markedly increased pro-apoptotic Bim and induced significant apoptosis compared to control siRNA-transfected cells, demonstrating novel role for MST1 and MST2 as pro-proliferative pro-survival proteins in human PAH. Immunocytochemical analysis revealed that, in contrast to nuclear localization in control cells, PAH PAVSMC had significant increase of cytoplasmic MST1 as evidenced by twice lower nucleus/cytoplasm ratio. Because phosphorylation of MST1 by Akt leads to MST1 cytoplasmic retention, we compared Akt-dependent T120-MST1 phosphorylation rates in control and diseased cells. We found that human PAH PAVSMC had significantly higher Akt-dependent T120-MST1 phosphorylation, marked up-regulation of Akt (assessed by P-S473) and reduced levels of Akt reciprocal effector FoxO1 compared to controls. Importantly, transfection of control PAVSMC with phosphomimetic T120D-MST1 and constitutively active myr-Akt1, but not myr-Akt2, induced MST1 cytoplasmic retention similar to what seen in PAH PAVSMC. Interestingly, siRNA-induced MST1 or MST2 knockdown significantly reduced S473-Akt phosphorylation and increased FoxO1 protein levels in PAH PAVSMC. Further, kinase-dead MST constructs suppressed S473-Akt phosphorylation, demonstrating that Akt activation in PAH PAVSMC requires active MST1 and 2. Confirming our in vitro data, smooth muscle-specific tamoxifen-induced depletion of Mst1/2 in mice with already developed SuHx-induced PH reversed pulmonary vascular remodeling and significantly reduced systolic right ventricular pressure (sRVP), pulmonary arterial pressure (PAP) and contractility (max dP/dT).

**Conclusion:** To the best of our knowledge, this is the first report of the pathological switch of MST1/2 function from anti-proliferative/pro-apoptotic to pro-proliferative/pro-survival protein. We also demonstrate that MST1/2 switch of function is associated with Akt1-induced MST1 cytoplasmic retention and, in turn, supports Akt up-regulation and FoxO1 deficiency and is required for maintenance
of disease-specific pro-proliferative/pro-survival PAVSMC phenotype and overall PH. This data suggest that MST1/2 may be explored as new highly selective remodeling-focused molecular targets in PAH.
121-B  Poster: Acetazolamide attenuates lung ischemia reperfusion injury by inhibiting proinflammatory cytokine release

Presenter: Akshay Kumar, Post-Doctoral Fellow

Research Interest: Translational
Pulmonary, Allergy and Critical Care Medicine

Mentors: Pablo Sanchez MD

Authors: Akshay Kumar MD, Tamara Cruz PhD, Nayra Cardenales PhD, John Sembrat, Maruicio Rojas MD, Pablo Sanchez MD

Introduction: Objective: Despite significant advancement to increase donor lung pool using Ex Vivo lung perfusion & DCD donors, ischemia reperfusion injury remains a notable complication leading to primary graft dysfunction as well as poor long term outcomes in lung transplantation. Acetazolamide (carbonic anhydrase inhibitor) has proven clinical utility in hypoxic pulmonary vasoconstriction (HPV) by possible inhibiting Ca2+ release from the sarcoplasmic reticulum. We tested whether it could also have a plausible role in protection against acute lung I/R injury in an animal model.

Methods: Sprague dawley rats (weighing 250-350gms) were divided into six groups 1] Sham (thoracotomy only) 2] Control (I/R injury with vehicle) 3] Treatment (I/R injury & pre-treatment with 30 mg/kg acetazolamide) 4] I/R Injury + NaHCO3 5] I/R Injury + 30 mg/kg Benzolamide 6] I/R Injury + 30mg/kg nmethyl AZA. For I/R injury left thoracotomy was done, lung ischemia was induced for 60 minutes by clamping the left hilum followed by reperfusion for 90 minutes. At the end of reperfusion, blood & BALF were collected for cytokine evaluation & histopathology of lung tissue was performed. Pulmonary vascular permeability was evaluated by Lung Wet/dry weight ratio and Gas exchange by measuring P/F ratio. BAL fluid protein quantification was done by BCA assay. Protein was extracted from lung tissue and analyzed for IL-6, TGF a, IL-17 & E-cadherin quantified using Image J software. Transcriptomic evaluation for pro-inflammatory cytokine TGF a, IL1b and IL6 was done by Power SYBR™ Green RNA-to-CT™ 1-Step method.

Results: Histopathology of lung showed marked inflammatory infiltrate, thickened interstitium & pulmonary edema due to I/R injury in the control compared to the Sham & treatment group. Pre-treatment with IV Acetazolamide (30 mg/kg) just prior to lung ischemia resulted in significantly decrease inflammatory response in the treated lungs. This was evidenced by the reduction in the levels of E cadherin in treatment group vs control grp ( p<0.005). Importantly, lungs from rats treated with AZA had maintenance of pulmonary vascular & endothelial integrity in contrast to control group. The plasma cytokine as well as the BALF cellular response was similarly blunted in the treatment group. BALF fluid protein was significantly lower in sham and treatment group compared to control group (p<0.01).Post reperfusion the lung gas exchange was better in the treatment group along with preservation of acid-base balance.

Conclusion: Our preliminary findings show that Acetazolamide can play a significant role in attenuating Lung ischemia reperfusion injury by inhibiting proinflammatory cytokine release and better preserve gas exchange. Thereby it can have potential therapeutic implications during Lung transplantation.
122-B  Poster: Age related cardiomyopathy in transgenic knock-in mouse model of sickle cell disease

Presenter: Maureen Mburu, Post-Doctoral Scholar

Research Interest: Translational VMI

Mentors: Flordeliza Villanueva MD

Funding Source: T32

Authors: Maureen Mburu MD, Samit Ghosh PhD, Xucai Chen PhD, Solomon Ofori-Acquah PhD, Flordeliza Villanueva MD

Introduction: Cardiopulmonary complications are the leading cause of death in sickle cell disease (SCD). Cardiac complications, including left ventricular (LV) dysfunction, are prevalent in both young and adult SCD patients. Our studies in the Townes transgenic murine model indicated that mice with homozygous SCD (SS) recapitulate the age-related clinical deterioration seen in humans. This was evidenced by the sudden decline in survival of SS mice during the transition from adolescence to adulthood, when the severity of intravascular hemolysis increased. We have also demonstrated that deficiency of the Nuclear factor erythroid-2-related factor 2 (Nrf2) in nonhematopoietic tissues of SS mice was associated with worsened intravascular hemolysis and organ damage. Therefore, we hypothesized that there is an age related SCD cardiomyopathy associated with worsening intravascular hemolysis.

Methods: Echocardiography of Townes SS mice and littermates with normal adult human hemoglobin A (AA mice) was performed using high resolution ultrasound at one, three, six and ten months of age. In separate groups, 3 cohorts of Nrf2−/− mice were transplanted with bone marrow cells from either SS or AA mice. SS donor littermates (SSWT) expressing Nrf2 were maintained as controls. Six months post engraftment, mice were imaged and plasma collected for analysis of intravascular hemolytic markers.

Results: Major differences in the cardiac phenotype were observed at six and ten months confirming SCD cardiomyopathy in SS. At ten months, the SS mice had larger LV internal dimensions, higher LV Mass Index (p=0.03), systolic (p<0.001) and diastolic volumes (p=0.002) compared to AA littermates. LV systolic dysfunction was evidenced by a decline in ejection fraction, with some SS mice exhibiting myocardial fibrosis histologically. Currently, we have confirmed successful engraftment in our first cohort of transplanted mice. SSNf2−/− mice (n=3) have reticulocytosis (p=0.005), lower hemoglobin (p=0.04) and RBC counts (p=0.002), compared to AANf2−/− mice (n=3). Concurrent with our age-related studies, SCD cardiomyopathy was confirmed at six months in the SSNf2−/− mice with larger LV internal diameter (p=0.008), higher LV diastolic volume (p=0.02), higher cardiac output (p=0.007), and higher stroke volume (p=0.049) compared to AANf2−/− littermates. In this preliminary cohort, SSNf2−/− did not demonstrate worsened intravascular hemolysis and hence cardiac phenotype, when compared to SSWT mice (n=2). Studies in larger cohorts are ongoing.

Conclusion: Our study shows progression of LV systolic dysfunction, LV enlargement and dilation in the SS mice. Studies in Nf2 knockout mice transplanted with SS marrow are ongoing to determine the contribution of non-hematopoietic Nrf2 in developing worsened cardiac phenotype in sickle mice.
**Introductions:** Evaluating donor grafts is one of the important elements in successful lung transplantation, but the objective measurable parameters are imperfect. Ex vivo lung perfusion (EVLP) opens another window to evaluate grafts initially declined with marginal quality, and allows potentially safe transplantation of those grafts. Clinical trials have suggested that EVLP has the potential to expand the donor pool and contribute 10-15%. Dynamic graft quality assessments are available during EVLP, however, no reliable biological indicators exist. Oxidative stress is involved in development of various organ diseases and triggers inflammatory cascade which affects posttransplant outcomes. Thus, we performed noninvasive reactive oxygen species (ROS) detection in perfusate during EVLP to assess graft oxidative status, and analyze how it may impact donor graft viability.

**Methods:** Cases of clinical EVLP performed at UPMC between September 2017 and July 2018 were included. The perfusate samples during EVLP were collected and analyzed by electron paramagnetic resonance (EPR) to detect circulating ROS. CMH. hydrochloride, an EPR spin probe, was used. EPR spectra were recorded using a Bruker X-band EMX premiumX spectrometer and normalized with ideal body weight and EVLP run time. All data were compared between lungs accepted or declined for transplantation on EVLP.

**Results:** 23 cases of EVLP were performed in the study term and the data of 18 cases were available for analysis. Donor characteristics were comparable in both groups. Mean EVLP run time was 196±57 min overall, and 176±94 and 204±31 min for declined and accepted lungs respectively. Of 18 lungs, 13 were accepted for transplantation (conversion rate: 72.2%). At the endpoint, no difference was observed on mean value of EVLP parameters between both groups. However, they were worsening with time in declined lungs but improved in accepted lungs. Also, there was no difference in the mean values of last PaO2/FiO2, but it was improved with time in both groups. Lab analysis for perfusate showed glucose consumption and lactate production in declined lungs were significantly higher than those of accepted lungs. Also, markedly higher EPR signals were detected in the perfusate from declined lungs compared to those from accepted lungs.

**Conclusion:** The assessment of oxidative status of grafts on EVLP using EPR spectroscopy suggested that declined lungs had higher oxidative stress. This may induce graft damage and edema thus leading to an unacceptable EVLP lung. Future interventions addressing inherent oxidative stress may afford improved graft condition during EVLP thereby potentially leading to successful lung transplantation.
**Poster:** Microbubbles carrying STAT3 Decoy Oligonucleotide with Pulsed Ultrasound for Enhanced Therapeutic Effect in Head and Neck Tumors

**Presenter:** Thiruganesh Ramasamy, Post-Doctoral Associate

**Research Interest:** Translational Cardiology

**Mentors:** Flordeliza S. Villanueva MD

**Funding Source:** NIH

**Authors:** Thiruganesh Ramasamy PhD, Xucai Chen PhD, Bin Qin PhD, Jennifer Grandis MD, Flordeliza S. Villanueva MD

**Introduction:** The signal transducer and activator of transcription 3 (STAT3) is an oncogenic transcription factor implicated in carcinogenesis, tumor progression, and drug resistance in many cancers, including head and neck squamous cell carcinoma (HNSCC). A new oligonucleotide (ODN) STAT3 decoy developed by our group offers a promising anti-tumor strategy, but achieving targeted tumor delivery of the decoy poses a significant challenge. We therefore sought to develop and compare two microbubble (MB) STAT3 decoy delivery vehicles loaded with decoy ODN in conjunction with ultrasound-targeted microbubble cavitation (UTMC) for tumor suppression.

**Methods:** Two types of MBs were prepared to load STAT3 decoy: cationic lipid-based MBs (C-MB) vs. liposome-loaded MBs (LPX) to enhance localized delivery of STAT3 decoy. To evaluate in vitro anticancer efficacy, human squamous carcinoma cell line CAL-33 cells were plated and incubated for 24 h. Cells were treated with ultrasound and respective MBs at a concentration equivalent to 10 MB/cell with MBs maximally loaded with 10 µg decoy in 1×10^9 MBs. Treatment efficacy was evaluated using a viability assay and apoptosis assay. Anticancer efficacy in vivo was performed in a CAL-33 tumor xenograft model in nude mice and evaluated in terms of tumor volume and survival rate.

**Results:** UTMC with both species of STAT3 decoy-loaded MB showed significantly more cytotoxicity compared to that of mutant control (p<0.05). UTMC in vitro with C-MB carrying STAT3 decoy showed significantly lower cell viability (p<0.05) of 56.8±8.4% compared to 84.5±8.8% for LPX in CAL-33 cell line, indicating superior therapeutic efficacy compared to the LPX formulation. Therefore, C-MB was used for all subsequent in vitro and in vivo experiments. STAT3 decoy-loaded MBs + UTMC caused significant (p<0.05) apoptosis of CAL33 cells. In vivo studies illustrated that UTMC with STAT3 decoy MB had strong antitumor effect, with significant reduction in the tumor burden compared to that of UTMC with decoy mutant-loaded MB and untreated animal groups (p<0.05), and with 100% of mice still surviving at day 15. Relative to the mutant control group, tumors in the STAT3 decoy-treated mice exhibited ~45% and ~38% (p<0.05) decreases in downstream target gene expression of Bcl-xL and cyclin D1, respectively, by protein analysis.

**Conclusion:** UTMC with STAT3 decoy-loaded MBs significantly reduced human tumor burden in xenograft mice, resulting in a higher survival rate compared to that of mutant decoy-treated and nontreated tumor-bearing animals. Our MB platform offers a promising image-guided, targeted delivery strategy for nucleotide-based therapeutics in cancer applications.
125-B  **Poster:** Single cell RNA sequencing identifies an ARDS monocyte response

**Presenter:** Brian Rosborough, Clinical Fellow

**Research Interest:** Translational
- Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Prabir Ray PhD

**Funding Source:** T32

**Authors:** Brian Rosborough MD, PhD, Yale Jiang BS, Jie Chen BS, Sarah Rapport MPH, Bryan McVerry MD, Wei Chen PhD, Anuradha Ray PhD, Prabir Ray PhD

**Introduction:** The acute respiratory distress syndrome (ARDS) is a common and fatal syndrome in the intensive care unit. ARDS is triggered by an inflammatory insult that causes recruitment of immune cells to the lungs resulting in epithelial and endothelial cell injury and respiratory failure. The precise immune mechanisms leading to the development of ARDS in at-risk patients is not well-defined.

**Methods:** Patients were recruited into the IRB-approved Acute Lung Injury Registry in the medical intensive care unit at the University of Pittsburgh. Peripheral blood mononuclear cells (PBMC) were collected from sex-matched patients with sepsis and pneumonia without ARDS (‘at-risk patients’) and patients with sepsis, pneumonia and ARDS (‘ARDS patients’). Single cell RNA sequencing was performed using the 10X Chromium platform to create single cell droplets. Single cell libraries were generated by reverse transcription followed by next generation sequencing. Samples consisted of 2500-4500 cells per patient with approximately 50,000 reads per cell. Cell populations were identified, and differential gene expression was analyzed.

**Results:** We successfully identified circulating leukocyte populations in the PBMC of at-risk and ARDS patients. Four distinct populations of circulating monocytes were identified. There was a differential response in the frequency of the monocyte sub-populations between at-risk patients and ARDS patients.

**Conclusion:** Single cell RNA sequencing of PBMC in ARDS patients reveals a unique peripheral immune signature defined by a differential response in monocyte populations. Further studies will be aimed at precisely defining the phenotype and function of these monocyte populations in ARDS.
126-B Poster: Change in Galectin-3 Level and Incidence of Cardiovascular Disease: Insights from the Atherosclerosis Risk in Communities Study

Presenter: Anum Saeed, Clinical Fellow

Research Interest: Translational Cardiology

Mentors: Christie Ballantyne MD

Funding Source: NIH R01

Authors: Anum Saeed MD, David Aguilar MD, Wensheng Sun MPH, Ron Hoogeveen PhD, Vijay Nambi MD, Elizabeth Selvin PhD, Kuni Matsushita MD, John McEvoy MD, Amil Shah MD, Sco Solomon MD, Eric Boerwinkle PhD, Christie Ballantyne MD

Introduction: Galactin-3 (Gal-3) is a marker of inflammation and fibrosis and has been implicated in the pathway of adverse cardiac remodeling as well as heart failure (HF). Data on association of Galactin-3 level changes with incident CVD (CHD, stroke and HF) is limited. Here we examined the association of galectin-3 levels at two different points of time with incident CVD events in the Atherosclerosis Risk in Communities (ARIC) study.

Methods: Plasma Gal-3 levels were examined (by chemiluminescent microparticle immunoassay [Abbott, Abbott Park, IL]) in a biracial cohort of 4159 men and women without prevalent CVD in ARIC study visit 4 (1996-98) and v5(2011-13). Delta change in Gal-3 (?Gal-3) was calculated and its associations (as categorical variable) with incident CHD, stroke, HF hospitalization were evaluated by Cox proportional hazards models, adjusted for CV risk factors, over mean follow-up of ~4.5 y. Quartile specific incident rates of CVD event (per 1000 person-years) were also calculated.

Results: Median change between v4(median age~62y) to v5(median age~74y) in Gal-3 was 2.7 (1.0, 5.0) ng/mL. Highest ?Gal-3 was seen in more Caucasians, hypertensive and diabetic individuals. Increasing (Q4vsQ1) ?Gal-3 had increased incidence rates of stroke (3.81 vs 6.94; p=0.04) and HF(7.23 vs 23.23 p<0.0001). Increasing change in Gal-3 was strongly associated with incident HF (HR=1.75[1.10-2.77]) and death (HR=1.59[1.14-2.22]) but not with CHD or stroke (Table).

Conclusion: Gal-3 levels increased with age and were strongly correlated to hypertension and diabetes mellitus in this cohort of biracial adults without baseline CVD. Further, increasing levels were significantly associated with risk of HF hospitalization and death. Further research is needed to examine whether aggressive preventive strategies can lower Gal-3 levels and risk of incident HF events.
**Poster: Pro-inflammatory B Cells Predict Progressive Minimal Early Renal Allograft Inflammation Which Is Associated With Poor Graft Outcomes**

**Presenter:** Akhil Sharma, Post-Doctoral Scholar

**Research Interest:** Translational
Renal-Electrolyte

**Mentors:** David Rothstein MD

**Funding Source:** T32

**Authors:** Akhil Sharma MD, Aravind Cherukuri MD, Rajil Mehta MD, Sundaram Hariharan MD, David Rothstein MD

**Introduction:** The clinical significance of minimal inflammation (MI: ‘t’=0, ‘i’>1) and Banff Borderline Changes (BBC: ‘t’ > 0 + ‘i’ = 1) in early renal allograft biopsies that does not meet criteria for acute rejection (AR, Banff = 1A) is unclear. The rate and significance of progression of these early lesions to late AR also remains unknown. In this study, we assessed the clinical significance of early tubulointerstitial inflammation (< Banff 1A rejection).

**Methods:** Our center performs 2 protocol biopsies (3 & 12 months) along with indication biopsies. This allowed us to assess the clinical impact of early (0-4 months) MI and BBC on graft outcomes. Furthermore, we examined the relationship between peripheral blood B cell cytokines and early MI and BBC.

**Results:** 208/372 patients transplanted between 1/13-11/14 had either no inflammation (NI, 36%, 76/208), MI (34%, 70/208) or BBC (30%, 62/208) on early biopsies (0-4 months). Patients with NI (17%), MI (24%) and BBC (34%) at 0-4 months exhibited increasing rates (in parentheses) of progression to AR (=Banff 1A) by 12mo. Further, patients with MI or BBC (0-4 months) had increased graft loss or impending graft loss (eGFR<30ml/min and >30% decline from baseline) by 50 months when compared to those with NI (p=0.01). While graft outcome in the NI group was not affected by progression to late AR (p=0.85), patients with early MI or BBC had significantly worse outcomes if they developed late AR. Thus, early allograft inflammation (either MI or BBC) was not only associated with increased progression to late AR, but those who progressed had worse outcomes. Thus, MI and BBC, particularly in patients who will progress to late AR, represent a clinical phenotype at risk for poor outcomes. Traditional clinical factors could not predict progression of MI or BBC to late AR. Based on previous results, we asked whether peripheral blood B cell cytokines could predict progression to AR in these patients. 72 patients with either MI (n=26) or BBC (n=46) had their B cells and cytokines analyzed at time of their early biopsy (2-4 months). IL-10:TNFa expression ratio within T1 transitional B cells was significantly lower in both the MI (6.3X ) and BBC (4.6X ) patients who progressed to late AR compared to those who did not (p<0.0004). Finally, a low T1 B cytokine ratio strongly predicted late progression to AR (ROC AUC 0.94 p<0.0001, Sen 92%, Spec 88%) in patients with early allograft inflammation (MI or BBC).

**Conclusion:** Patients with early allograft inflammation that progress to AR by 1 year represent a high-risk cohort for graft dysfunction. This group could be identified by 2-4 mo, using the T1 B IL-10:TNFa ratio – allowing early intervention.
128-B  **Poster:** Alteration in oral and gut microbiome associated with HIV co-infections  

**Presenter:** Libing Yang, Health Science Research Fellow  

**Research Interest:** Translational  
Pulmonary, Allergy and Critical Care Medicine  

**Mentors:** Alison Morris MD  

**Funding Source:** R01  

**Authors:** Libing Yang MD, Daniel Dunlap MD, Adam Fitch BS, S. Mehdi Nouraei MD, Arlene Bullotta BS, Yue Chen PhD, Charles Rinaldo PhD, Barbara Methé PhD, Alison Morris MD  

**Introduction:** Despite of the success of antiretroviral therapy (ART), people with HIV (PWH) are at high risk co-infection with viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human herpesvirus-8 (HHV-8). HIV co-infections play a role in the pathogenesis of HIV co-morbidities, but the underlying mechanisms are not fully understood. Studies showed that PLW have different bacterial microbiota compositions and associated host responses compared to HIV-uninfected individuals. It is also possible that HIV co-infections might alter microbiome and immune responses in PLW. We collected oral and gut samples and determined relationships of microbiome to HIV viral co-infections.  

**Methods:** We recruited 69 male participants with chronic HIV infections on virus-suppressive ART in the Pittsburgh site of the Multicenter AIDS cohort study. We used serologic tests for HBV, HCV, HHV-8, herpes simplex virus-1 (HSV-1) and HSV-2 and performed PCR for GB virus C (GBV-C). Sequencing of bacterial 16S rRNA gene was performed to characterize microbiome composition. Data was processed and analyzed using mothur and R.  

**Results:** Among all participants, 36 PLW had HBV infection and 3 had HCV infection. In 22 participants with available HHV-8 tests, 12 PLW had HHV-8 infection. In 17 participants with available tests results, 2 PWH had HSV-1 infection and 3 had HSV-2 infection. Only 7 participants were tested for GBV-C, and 3 of them had positive results. In saliva samples, HBV, HHV-8 and HSV-1 was associated with alterations in the oral microbiome. Beta diversity of the oral microbiome differed among individuals with resolved HBV infection, those with chronic HBV infection and HBV-uninfected individuals (PERMANOVA, p-value=0.002, R2=0.1). PLW with HHV-8 or HSV-1 infection had a higher alpha diversity compared to those without (by Shannon index, p-value=0.04; p-value=0.003, respectively). Bacteria associated with co-infections included potential pathogens such as Pseudomonadaceae, Aggregatibacter and Mycoplasma, as well as oral commensals such as Prevotellaceae and Lactobacillus. In stool samples, alpha diversity of the gut microbiome in GBVC-infected PLW was higher than that in GBVC-uninfected PLW (p-value=0.03).  

**Conclusion:** Oral microbiome alterations were associated with HIV co-infections including HBV, HHV-8 and HSV-1. Virus-associated differences in the gut microbiome were less clear, with the only exception of alpha diversity by GBV-C status. Higher alpha diversity was seen in PLW with co-infections, possibly secondary to immune suppression associated with viral co-infection. These results indicate HIV co-infections may be associated with alterations in the host microbiome, but relationship to co-morbidities remains to be determined.
**129-B  Poster:** Alterations in Oral and Gut Microbiota in HIV-infected Individuals Related to Pulmonary Function

**Presenter:** Libing Yang, Health Science Research Fellow

**Research Interest:** Translational Pulmonary, Allergy and Critical Care Medicine

**Mentors:** Alison Morris MD

**Funding Source:** R01

**Authors:** Libing Yang MDc, Daniel Dunlap MD, Adam Fitch MS, Kelvin Li MS, Carl Koch MD, S. Mehdi Nouraie MD, Rebecca DeSensi BA, Ken Ho MD, Jeremy Martinson PhD, Barbara Methé PhD, Alison Morris MD

**Introduction:** HIV infection is an independent risk factor for chronic obstructive pulmonary disease (COPD), but the mechanisms involved are poorly understood. Because HIV infection impacts the immune system, alterations in the microbiome have been proposed as mechanisms of disease development or progression. Studies have demonstrated that HIV infection is associated with dysbiosis in saliva. The lung microbiome is largely derived from the oral microbiome via aspiration, but whether the oral dysbiosis associated with HIV correlates with COPD has yet to be determined. In addition, the gut microbiome may influence lung disease, but this relationship has not been investigated in HIV. We collected oral and gut samples from individuals with and without HIV infection and determined relationships of bacterial communities to lung function.

**Methods:** 75 HIV-infected and 93 HIV-uninfected men participating in the Pittsburgh site of the Multicenter AIDS cohort study (MACS) performed pre- and post-bronchodilator spirometry and diffusing capacity for carbon monoxide (DLCO) per guidelines and had oral and stool samples collected. Sequencing of the 16S rRNA gene on Illumina MiSeq platform was performed to characterize the composition of oral and gut microbiota. Sequences were analyzed using mothur and R.

**Results:** In saliva samples, the oral microbiome composition differed between HIV-infected and HIV-uninfected individuals (Permanova for Bray-Curtis distance, p-value=0.0007). Within the HIV-infected group, differences were seen in individuals with reduced lung function as compared to those with normal function. These differences included profile alterations (p-value=0.015) and lower alpha diversity (by Shannon index, t-test p-value=0.033) between individuals with reduced DLCO (<80% predicted) and those without, as well as a significant difference in oral microbiome composition between those with normal versus low (<70%) post-bronchodilator forced expiratory volume in one second/forced vital capacity [FEV1/FVC] (p-value=0.036). We noted significantly increased levels of Veillonella, Streptococcus, Lactobacillus and decreased levels of Prevotella, Fusobacterium in HIV-infected individuals with abnormal lung function. However, among HIV-uninfected individuals, microbiome communities were taxonomically similar between groups with and without reduced DLCO or FEV1/FVC. The gut microbiome communities of HIV-infected individuals were similar to those of HIV-uninfected, and there was no relationship to lung function in either group.

**Conclusion:** Next-generation sequencing analysis identified oral microbiota alterations in HIV-infected individuals. Profound changes in the oral microbiome profile were observed in HIV-infected individuals with abnormal lung function, but not in HIV-uninfected individuals, suggesting a unique role of the microbiome in the pathogenesis of chronic lung diseases in HIV.
**130-B Poster:** Ultrasound-targeted microbubble cavitation with sodium nitrite synergistically enhances nitric oxide production and microvascular perfusion

**Presenter:** Gary Yu, Graduate Student

**Research Interest:** Translational Cardiology

**Mentors:** John Pacella MD

**Funding Source:** T32

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**Introduction:** Congestive heart failure following AMI is rising due to microvascular obstruction (MVO), a combination of obstruction by atherothrombotic debris and inflammation accentuated by decreased nitric oxide bioavailability. We previously demonstrated that ultrasound-targeted microbubble cavitation (UTMC) may relieve MVO and increase endogenous NO production. We hypothesized that co-administration of nitrite, a source of exogenous NO, would enhance the therapeutic effects of UTMC through increasing NO bioavailability and microvascular perfusion.

**Methods:** UTMC was delivered to a rat hindlimb using lipid microbubbles sonicated by therapeutic ultrasound pulses for 2 minutes. In select groups, sodium nitrite and/or N-Nitro-L-arginine methyl ester (L-NAME), an eNOS inhibitor, were given 5 minutes prior to UTMC. An intramuscular NO probe was placed for real-time concentration measurements to 30 minutes post-UTMC. Microvascular blood volume was measured using contrast ultrasound with infusion of Definity microbubbles at baseline, 3, 6, 10, and 30 minutes post-UTMC. Treatment effects were evaluated using a mixed effect model with a Bonferroni correction.

**Results:** Treatment factors of UTMC, nitrite, and L-NAME had significant interactions. UTMC and nitrite together showed significantly increased blood volumes at all observation points compared to baseline and UTMC alone. Addition of LNAME to UTMC and nitrite resulted in decreased blood volume at 3, 10, and 30 minutes below baseline. Similar results were seen in NO concentration, where UTMC and nitrite resulted in significant increases above either UTMC or nitrite alone that were ablated with LNAME.

**Conclusion:** We have shown that UTMC and nitrite therapy results in synergistic improvements of microvascular blood volume and NO concentration that are partially dependent on eNOS activity. These results provide mechanistic insight into UTMC and means of enhancing its efficacy through increasing NO bioavailability.
Introduction: Radiation cystitis results from radiation therapy for pelvic tumors and accounts for up to 7% of emergency urology admissions. It can be classified into acute and chronic stages where the former is characterized by urothelial layer disruption and inflammation. Current therapies are limited, invasive and often fail to demonstrate optimal efficacy. Radiation damage is mediated by reactive oxygen and nitrogen species. Our findings suggest that the principal site of radiation-induced free radical generation in the bladder is urothelial mitochondria and free radical scavengers are radioprotective. We have also demonstrated that small molecule mediators of p75 proneurotrophin receptor (p75NTR), a key initiator of the apoptotic cascade, prevented irradiation-induced bladder damage and increased survival and growth of the urothelial cells. In this study we examined the efficacy of combination therapy including a mitochondrially-targeted free radical scavenger, XJB-5-131, and a selective p75NTR blocker, LM11A-31.

Methods: Mice were anesthetized with avertin (300 mg/kg, IP). The bladders were emptied via a transurethral catheter and 100 µl of 1 µM XJB-5-131 or vehicle (1% DMSO) instilled. The bladders were selectively irradiated by a focused 10 mm wide X-ray beam while they were withdrawn through an incision in the abdominal cavity to avoid damage to surrounding organs. Following irradiation (10 Gy), the animals were allowed to recover with prophylactic analgesic and antibiotics. LM11A-31 (10 mg/kg/day) was gavaged starting a day before irradiation. A day after irradiation, mice were euthanized, bladders excised, mounted on nylon rings (0.09 cm² exposed area) and placed in Ussing chambers with oxygenation and temperature control (n=3 in each group) for transepithelial resistance (TER) determination. Bladder tissues were also fixed in 10% PFA, embedded in paraffin, cut 3 µm thick and stained with H&E for histological analysis.

Results: Urothelial damage is associated with dramatic decreases in TER, exposing the bladder wall to toxic compounds in urine resulting in inflammation. One day following irradiation, bladder TER decreased from 8,372 ± 1,868 to 732 ± 187 Ohm·cm². XJB-5-131 instillation alone increased TER to 1,641 ± 100 Ohm·cm², LM11A-31 treatment, to 5,696 ± 490 Ohm·cm² and their combination, to 9,142 ± 403 Ohm·cm² completely restoring the urothelial barrier. Histological evaluation of bladder wall sections revealed irradiation-induced disruption of urothelial cell layer in untreated animals but not in animals that received the combination therapy.

Conclusion: A selective p75NTR blocker in combination with a mitochondrially-targeted free radical scavenger were synergistic in treating acute irradiation-induced bladder damage and may contribute to improvement in long-term organ function.
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